

The American Journal of Cardiology

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AUGUST 1, 1990

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A YORKE MEDICAL JOURNAL/CAHNERS PUBLISHING COMPANY

250 TOTAL

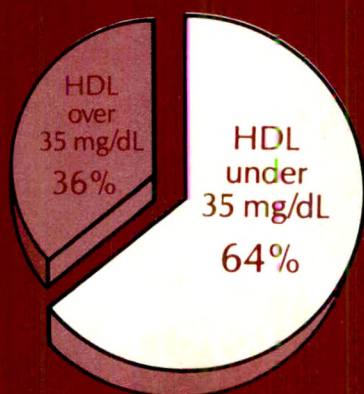
<35 HDL

mg/dL

What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol and triglycerides—are common among heart attack victims,¹ and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.²

HEART ATTACK PATIENTS
(PROCAM TRIAL)²



The American Journal of Cardiology

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CORONARY ARTERY DISEASE**251****Secondary Prevention After High-Risk Acute Myocardial Infarction with Low-Dose Acebutolol**

Jean-Pierre Boissel, Alain Leizorovicz, Hélène Picolet, and Jean-Claude Peyrieux for the APSI Investigators

This double-blind, placebo controlled trial was designed to test the effect of acebutolol, a β blocker with mild intrinsic sympathomimetic activity in high-risk postacute myocardial infarction patients. Six hundred seven patients were included. The 1-year mortality in the placebo group was 12.4%. With an average follow-up of 318 days, the total mortality decrease was 48% and the vascular mortality decrease was 58%.

261**Improved Survival but not Left Ventricular Function with Early and Prehospital Treatment with Tissue Plasminogen Activator in Acute Myocardial Infarction**

Gabriel I. Barbash, Arie Roth, Hanoch Hod, Hilton I. Miller, Michaela Modan, Shemuel Rath, Yedahel Har Zahav, Amir Shachar, Shemuel Basan, Alexander Battler, Michael Motro, Babeth Rabinowitz, Elieser Kaplinsky, Uri Seligsohn, and Shlomo Laniado

One hundred ninety patients with acute myocardial infarction received recombinant tissue-type plasminogen activator 2.0 ± 0.8 hours after the onset of symptoms. Patients treated within 2 hours of symptom onset had significantly lower short- and long-term mortality. Prehospital initiation of rt-PA treatment appears to be safe and feasible and resulted in a 40-minute decrease in the time from symptom onset to treatment initiation.

267**Effects of Early Intervention with Low-Dose Aspirin (100 mg) on Infarct Size, Reinfarction and Mortality in Anterior Wall Acute Myocardial Infarction**

Freek W.A. Verheugt, Arnoud van der Laarse, Albert J. Funke-Kupper, Luc G.W. Sterkman, Tjebbe W. Galema, and Jan P. Roos

In a prospective, randomized placebo-controlled trial, the influence of early intervention with low-dose aspirin (100 mg daily given for 3 months) on infarct size (cumulative plasma lactate dehydrogenase release) and clinical outcome was studied in 100 consecutive patients with first anterior wall acute myocardial infarction. Early aspirin decreased infarct size by about 10% and 3-month mortality was also lower in the aspirin group, but these differences were not statistically significant. Our data indicate that the effect of early aspirin on mortality in acute myocardial infarction, as reported in large trials, is probably due more to prevention of reinfarction than to decrease of infarct size.

271**Beneficial Effect of Magnesium Sulfate in Acute Myocardial Infarction**

Michael Shechter, Hanoch Hod, Nila Marks, Shlomo Behar, Elieser Kaplinsky, and Babeth Rabinowitz

The effects of magnesium on the incidence of arrhythmias and on mortality were evaluated in 103 patients with documented acute myocardial infarction in a randomized, double-blind, placebo-controlled study. Fifty patients received a magnesium infusion for 48 hours and 53 received placebo. No adverse effects were observed during and after magnesium infusion; these data support a possible protective role of magnesium in patients with AMI.

275**Effect of Dipyridamole at the Usual Oral Dose on Exercise-Induced Myocardial Ischemia in Stable Angina Pectoris**

Tsuneo Tsuya, Michio Okada, Hiroo Horie, and Kyoza Ishikawa

We performed a randomized, double-blind, placebo-controlled crossover study to investigate the effect of dipyridamole at a usual oral dose of 150 mg/day on 18 patients with angina pectoris. The degree of ST depression and the threshold for angina pectoris in the treadmill exercise electrocardiography, which was performed on the last days of dipyridamole and placebo administration, were compared. A usual oral dose of dipyridamole induced myocardial ischemia during exercise in some patients, while it improved it in a similar number of patients.

279**Reduction of Myocardial Ischemia During Percutaneous Transluminal Coronary Angioplasty with Oxygenated Fluosol®**

Kenneth M. Kent, Michael W. Cleman, Michael J. Cowley, Mervyn B. Forman, C. Carl Jaffe, Marvin Kaplan, Spencer B. King III, Mitchell W. Krucoff, Thomas Lassar, Bruce McAuley, Rafael Smith, Charlene Wisdom, and Daniel Wohlgeleirter

In a multicenter trial of 245 patients, we examined the effects of a perfluorochemical emulsion (Fluosol®) on myocardial ischemia during percutaneous transluminal coronary angioplasty. Perfusion with Fluosol is effective in alleviating myocardial ischemia during angioplasty and can be safely administered in this patient population.

Outcome Following Emergency Coronary Artery Bypass Grafting for Failed Elective Balloon Coronary Angioplasty in Patients with Prior Coronary Bypass

Joel K. Kahn, Barry D. Rutherford, David R. McConahay, Warren L. Johnson, Lee V. Giorgi, Thomas M. Shimshak, and Geoffrey O. Hartzler

What are the frequency and outcome of emergency coronary artery bypass grafting for failed angioplasty in patients with prior CABG? We assessed these in 2,136 elective angioplasty procedures in prior CABG patients. Emergency CABG after failed angioplasty in patients with prior CABG is required infrequently; in patients without extreme high-risk features, emergency repeat CABG can be accomplished with good hospital and long-term results.

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Role of Tricuspid Regurgitation and Left Ventricular Damage in the Treatment of Right Ventricular Infarction-Induced Low Cardiac Output Syndrome

Jean-François Dhainaut, Emmanuel Ghannad, Didier Villemant, Fabrice Brunet, Jean-Yves Devaux, Bruno Schremmer, Pierre Squara, Simon Weber, and Julien-François Monsallier

The effect of tricuspid regurgitation and extensive left ventricular infarction and its influence on the treatment response were studied in 20 patients with right ventricular myocardial infarction, 5 of whom had severe tricuspid regurgitation and 8 of whom had depressed LV function. Volume loading increased cardiac output slightly in all patients. Dobutamine, which improved right ventricular function and consequently LV preload, was especially efficacious in patients with depressed LV function.

296

The Divergent Recovery of ST-Segment Depression and Radionuclide Angiographic Indicators of Myocardial Ischemia

Pierce J. Vatterott, Peter C. Hanley, Harold T. Mankin, and Raymond J. Gibbons

We evaluated the recovery after exercise of both electrocardiographic ST-segment depression and exercise-induced abnormalities in regional wall motion and ejection fraction in 31 patients who had persistent ST-segment depression after exercise. Radionuclide angiographic evidence of ischemia recovers more quickly after exercise than ST-segment depression.

302

Acute Coronary Vasomotor Effects of Nifedipine and Therapeutic Correlates in Syndrome X

Piero Montorsi, Sergio Cozzi, Alessandro Loaldi, Franco Fabbicocchi, Alvise Polese, Nicoletta De Cesare, and Maurizio D. Guazzi

In 18 patients with syndrome X, 10 mg sublingual nifedipine significantly increased coronary artery diameter, blood flow and plasma norepinephrine concentration and decreased coronary resistance and ST-segment response to exercise. After 4 weeks of treatment with nifedipine (10 to 20 mg, 4 times daily), the ST-segment response to exercise was further improved concomitantly with a decrease in norepinephrine plasma concentrations. Thus, nifedipine exerts a beneficial effect in syndrome X through coronary vasodilatation; reflex activation of the adrenergic system may, in some cases, restrict the therapeutic effect of the drug in the short-term treatment but not in the long-term treatment.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

308

Relation Between Ventricular Late Endocardial Activity During Intraoperative Mapping and Low-Amplitude Signals Within the Terminal QRS Complex on the Signal-Averaged Surface Electrocardiogram

Hans-Joachim Schwarzmaier, Ulrich Karbenn, Martin Borggrefe, Jörg Ostermeyer, and Günter Breithardt with the technical assistance of Klaus Balkenhoff

We performed noninvasive recording of ventricular late potentials and intraoperative endocardial mapping at 36 sites in 24 patients with left ventricular aneurysm and drug-resistant sustained ventricular tachycardia due to coronary artery disease. For detection of late potentials on the signal-averaged QRS complex, 3 different algorithms were used. Patients with a late potential showed a higher number of recordings exceeding a given endocardial delay than patients without (5.5, 5.5, and 5.6 sites vs 2.4, 1.1, and 0.9 sites). They also exhibited an increased mean endocardial delay (38, 35, and 37 ms vs 20, 19, and 11). There was no correlation between the duration or amplitude of the late potential, if present, and the number of endocardial sites exhibiting delayed activity or the mean duration of the endocardial delayed activity. These results indicate that the presence of late potentials on the signal-averaged surface ECG is related to the mean duration of endocardial late activity as well as to the number of endocardial sites exhibiting a given degree of delayed activation. Thus, it is dependent on the mass of slowly activated tissue.

CONGESTIVE HEART FAILURE

315

Studies of Left Ventricular Dysfunction (SOLVD)—Rationale, Design and Methods: Two Trials That Evaluate the Effect of Enalapril in Patients with Reduced Ejection Fraction

The SOLVD Investigators

The Studies of Left Ventricular Dysfunction is an integrated research program of patients with low ejection fraction or congestive heart failure. The program includes 2 clinical trials, 1 in symptomatic and 1 in asymptomatic patients, of the effectiveness of enalapril on mortality. In addition, a registry of patients with left ventricular dysfunction has been established.

323

Radial Arterial Pressure Measurements May Be a Poor Guide to the Beneficial Effects of Nitroprusside on Left Ventricular Systolic Pressure in Congestive Heart Failure

Gerald J. Simkus and David H. Fitchett

We studied the effect of nitroprusside on central aortic and peripheral radial arterial pressures in 10 patients with severe congestive heart failure. Our results show that nitroprusside does not reduce peripheral and aortic systolic pressure equally. We suggest that peripheral pressure measurements for the assessment of left ventricular afterload must be used cautiously, especially in patients who are receiving vasodilator therapy.

VALVULAR HEART DISEASE

327

Early and Late Changes in Left Ventricular Systolic Performance After Percutaneous Aortic Balloon Valvuloplasty

David H. Harpole, Charles J. Davidson, Thomas N. Skelton, Katherine B. Kisslo, Robert H. Jones, and Thomas M. Bashore

Seventeen patients underwent radionuclide angiography with simultaneous high-fidelity micromanometer pressure before, 10 minutes after and 6 months after aortic valvuloplasty. Immediately after the procedure, the mean and peak aortic transvalvular gradient decreased and aortic valve area increased. There were little data to support an intrinsic change in myocardial contractile performance at any postprocedural interval after aortic valvuloplasty; the changes in hemodynamics are primarily the function of altered loading conditions.

333

Detection and Assessment of Severity of Tricuspid Regurgitation Using First-Pass Radionuclide Angiography and Comparison with Pulsed Doppler Echocardiography

Kim A. Williams, Patricia E. Walley, and James W. Ryan

Using first-pass radionuclide angiography, we performed non-invasive detection and semiquantitative assessment of tricuspid regurgitation in 51 patients. Right atrial "injection fraction" during first-pass RNA allows detection and grading of the severity of TR, with results very similar to pulsed Doppler echocardiography.

CONGENITAL HEART DISEASE

340

Long Follow-Up (to 43 Years) of Ventricular Septal Defect with Audible Aortic Regurgitation

Larry A. Rhodes, John F. Keane, John P. Keane, Kenneth E. Fellows, Richard A. Jonas, Aldo R. Castaneda, and Alexander S. Nadas

From 1946 to March 1989, 92 patients (33 women and 59 men) were seen with ventricular septal defect and audible aortic regurgitation. The VSD was subcrystal in 62 patients, subpulmonary in 21 and unknown in the remaining 9; the median age of onset of aortic regurgitation was 5.3 years and the risk of developing it was 2.5 times greater in those with a subpulmonary VSD. Procedures consisted of VSD closure alone in 7 patients, VSD closure and valvuloplasty in 50 and VSD closure and aortic valve replacement in 15; the degree of AR was more effectively decreased by valvuloplasty in those operated on under the age of 10.

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Frequency and Prognosis of Arrhythmias After Operative "Correction" of Tetralogy of Fallot

Guy Vaksman, Anne Fournier, André Davignon, Gilles Ducharme, Lucile Houyel, and Jean-Claude Fouron

We followed 224 consecutive patients operated on for tetralogy of Fallot from 1 to 28 years (mean 11). Mean age at surgery was 5.3 years (range 1 to 14). Twenty-four-hour ambulatory monitoring in 92 patients demonstrated significant ventricular arrhythmias (\geq grade 2 of the Lown grading system) in 41 (45%). Incidence of ventricular arrhythmia correlated with length of follow-up and duration of cardiopulmonary bypass. There were no sudden deaths. Systematic treatment of postoperative ventricular arrhythmias in tetralogy of Fallot should be reconsidered.

350

An Electrocardiographic Midterm Follow-Up Study After Anatomic Repair of Transposition of the Great Arteries

Juan Villafane, Sara White, Francisco Elbl, Allan Rees, and Robert Solinger

Prospective studies of rhythm and conduction, before and after 1-stage anatomic repair of simple transposition of the great arteries, were performed on 24 survivors. Asymptomatic low-grade atrial and ventricular ectopic activity was infrequently observed in 24-hour electrocardiograms performed 1, 2, 3 and 4 years after surgery. After a mean follow-up of 3 years, all of our patients remain in sinus rhythm.

MISCELLANEOUS

355

Safety of Cardiac Angiography with Conventional Ionic Contrast Agents

John W. Hirshfeld, Jr., William G. Kussmaul, Peter M. DiBattiste, and the Investigators of the Philadelphia Area Contrast Agent Study

We gathered data on the frequency of adverse reactions to conventional contrast agents in 4,630 cardiac angiographic procedures. The adverse reaction rate was 14.2% for minor and 1.3% for major events; there were no deaths. Patients with higher New York Heart Association classes and elevated left ventricular end-diastolic pressure had the most adverse reactions. Cardiac angiography can be performed safely in most patients with conventional high osmolality ionic contrast agents.

362

Self-Efficacy and In-Patient Cardiac Rehabilitation

Neil B. Oldridge and Barbara L. Rogowski

Fifty-one cardiac patients were randomized to either a ward ambulation program or a dedicated exercise center before hospital discharge to assess changes in self-efficacy. Of the many variables tested, the dedicated exercise center patients had higher self-efficacy scores for walking time and overall exertion only. These 2 types of in-patient exercise programs appear to be equally effective but the lower cost of the ward ambulation program suggests it is more cost-effective.

EDITORIALS

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Usefulness of Echocardiography in Managing Left Ventricular Thrombi After Acute Myocardial Infarction

Dennis A. Plante and Paul T. Vaitkus

Corrections**INSTRUCTIONS TO AUTHORS** on page 384**CLASSIFIED ADVERTISING** on pages A72, A73

CardioGen-82*
Rubidium Rb 82 Generator

INDICATIONS AND USAGE

Rubidium chloride Rb 82 injection is a myocardial perfusion agent that is useful in distinguishing normal from abnormal myocardium in patients with suspected myocardial infarction.

Cardiogen-82 (Rubidium Rb 82 Generator) must be used with an infusion system specifically labeled for use with the generator and capable of accurate measurement and delivery of doses of rubidium chloride Rb 82 injection not to exceed a single dose of 2220 MBq (60 mCi) and a cumulative dose of 4440 MBq (120 mCi) at a rate of 50 mL/min with a maximum volume per infusion of 100 mL and a cumulative volume not to exceed 200 mL. These performance characteristics reflect the conditions of use under which the drug development clinical trials were conducted.

Adequate data from clinical trials to determine precise localization of myocardial infarction or identification of stress-induced ischemia have not been collected.

Positron emission tomographic (PET) instrumentation is recommended for use with rubidium chloride Rb 82 injection.

CONTRAINDICATIONS

None known.

WARNINGS

Caution should be used during infusion as patients with congestive heart failure may experience a transitory increase in circulatory volume load. These patients should be observed for several hours following the Rb-82 procedure to detect delayed hemodynamic disturbances.

PRECAUTIONS

General

Data are not available concerning the effect of marked alterations in blood glucose, insulin, or pH (such as is found in diabetes mellitus) on the quality of rubidium chloride Rb 82 scans. Attention is directed to the fact that rubidium is physiologically similar to potassium, and since the transport of potassium is affected by these factors, the possibility exists that rubidium may likewise be affected.

Rubidium chloride Rb 82 injection must be administered only with an appropriate infusion system capable of meeting the performance characteristics previously described. (See **INDICATIONS AND USAGE**). The drug should be used only by those practitioners with a thorough understanding of the use and performance of the infusion system.

Repeat doses of rubidium chloride Rb 82 injection may lead to an accumulation of the longer lived radioactive contaminants strontium Sr 82 and strontium Sr 85.

Since eluate obtained from the generator is intended for intravenous administration, aseptic techniques must be strictly observed in all handling. Only additive free Sodium Chloride Injection USP should be used to elute the generator. Do not administer eluate from the generator if there is any evidence of foreign matter.

As in the use of any radioactive material, care should be taken to minimize radiation exposure to the patient consistent with proper patient management and to insure minimum radiation exposure to occupational workers.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed to evaluate carcinogenic potential, mutagenicity potential, or to determine whether rubidium Rb 82 may affect fertility in males or females.

Pregnancy Category C

Animal reproductive studies have not been conducted with rubidium Rb 82. It is also not known whether rubidium Rb 82 can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Rubidium Rb 82 should be given to pregnant women only if the expected benefits to be gained clearly outweigh the potential hazards.

Ideally, examinations using radiopharmaceuticals, especially those examinations which are elective in nature, in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.

Nursing Mothers

It is not known whether rubidium Rb 82 is excreted in human milk. Due to the short half-life of rubidium Rb 82 (75 sec) it is unlikely that the drug would be excreted in human milk during lactation. However, because many drugs are excreted in human milk, caution should be exercised when rubidium Rb 82 is administered to nursing women.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

No adverse reactions specifically attributable to rubidium Rb 82 have been reported during controlled clinical trials.

HOW SUPPLIED

Cardiogen-82 (Rubidium Rb 82 Generator) is supplied in the form of strontium Sr 82 adsorbed on a hydrous stannic oxide column with an activity of 90-150 millicuries Sr-82 at calibration time. The generator is encased in a lead shield surrounded by a labeled plastic container. Complete assay data for each generator are provided on the container label. Cardiogen-82 (Rubidium Rb 82 Generator) is intended for use only with an appropriate, properly calibrated infusion system labeled for use with the generator.

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CORONARY ARTERY DISEASE

251**Secondary Prevention After High-Risk Acute Myocardial Infarction with Low-Dose Acebutolol**

Jean-Pierre Boissel, Alain Leizorovicz, Hélène Picolet, and Jean-Claude Peyrieux for the APSI Investigators

This double-blind, placebo controlled trial was designed to test the effect of acebutolol, a β blocker with mild intrinsic sympathomimetic activity in high-risk postacute myocardial infarction patients. Six hundred seven patients were included. The 1-year mortality in the placebo group was 12.4%. With an average follow-up of 318 days, the total mortality decrease was 48% and the vascular mortality decrease was 58%.

261**Improved Survival but not Left Ventricular Function with Early and Prehospital Treatment with Tissue Plasminogen Activator in Acute Myocardial Infarction**

Gabriel I. Barbash, Arie Roth, Hanoch Hod, Hilton I. Miller, Michaela Modan, Shemuel Rath, Yedahel Har Zahav, Amir Shachar, Shemuel Basan, Alexander Battler, Michael Motro, Babeth Rabinowitz, Elieser Kaplinsky, Uri Seligsohn, and Shlomo Laniado

One hundred ninety patients with acute myocardial infarction (AMI) were treated with recombinant tissue-type plasminogen activator (rt-PA) 2.0 ± 0.8 hours after the onset of symptoms. Eighty-seven patients enrolled via mobile intensive care units and 103 through the emergency ward. All 190 patients except 2 underwent delayed coronary angiography and, when indicated, angioplasty 72 hours after enrollment. Patients treated within 2 hours and those treated 2 to 4 hours after symptom onset had similar preservation of left ventricular function, and similar prevalence of congestive heart failure at discharge. Patients treated within 2 hours of symptom onset had significantly lower short- (0 vs 6%, $p = 0.01$) and long-term (1 vs 10%, $p = 0.03$) mortality. Prehospital initiation of rt-PA appeared to be safe and feasible and resulted in a 40-minute decrease in the time from symptom onset to treatment initiation.

Continued on page A17

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Effects of Early Intervention with Low-Dose Aspirin (100 mg) on Infarct Size, Reinfarction and Mortality in Anterior Wall Acute Myocardial Infarction

Freek W.A. Verheugt, Arnoud van der Laarse, Albert J. Funke-Küpper, Luc G.W. Sterkman, Tjebbe W. Galema, and Jan P. Roos

In a prospective, randomized placebo-controlled trial, the influence of early intervention with low-dose aspirin (100 mg daily given for 3 months) on infarct size (cumulative plasma lactate dehydrogenase release) and clinical outcome was studied in 100 consecutive patients with first anterior wall acute myocardial infarction. Early aspirin decreased infarct size by about 10% and 3-month mortality was also lower in the aspirin group, but these differences were not statistically significant. However, reinfarction occurred significantly less in the aspirin patients. Therefore, the effect of early aspirin on mortality in acute myocardial infarction, as reported in the large trials, is probably due more to prevention of reinfarction than to decrease of infarct size.

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Beneficial Effect of Magnesium Sulfate in Acute Myocardial Infarction

Michael Shechter, Hanoch Hod, Nila Marks, Shlomo Behar, Elieser Kaplinsky, and Babeth Rabinowitz

The effects of magnesium on the incidence of arrhythmias and on mortality were evaluated in 103 patients with documented acute myocardial infarction (AMI) in a randomized, double-blind, placebo-controlled study. Fifty patients received a magnesium infusion for 48 hours and 53 received placebo. The baseline characteristics of the population were similar in the 2 groups. Tachyarrhythmias requiring drug therapy were recorded in 32% of the patients in the magnesium group and in 45% of the placebo group. Conduction disturbances were found in 23% of the placebo group as compared to 14% in the magnesium group. The intrahospital mortality was 2% (1 patient) in the magnesium group compared to 17% (9 patients) in the placebo group ($p < 0.01$). No adverse effects were observed during and after the magnesium infusion. These data support a possible protective role of magnesium in patients with AMI.

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Effect of Dipyridamole at the Usual Oral Dose on Exercise-Induced Myocardial Ischemia in Stable Angina Pectoris

Tsuneo Tsuya, Michio Okada, Hiroo Horie, and Kyoza Ishikawa

A randomized, double-blind, placebo-controlled crossover study was performed to investigate the effect of dipyridamole at a usual oral dose of 150 mg/day on 18 patients with angina pectoris. The degree of ST depression and the threshold for angina pectoris in the treadmill exercise electrocardiography, which was performed on the last days of dipyridamole and placebo administration, were compared. Dipyridamole caused an aggravating effect on the ST change in 3 patients and a salutary effect in 5 patients. Dipyridamole decreased the threshold for angina pectoris in 5

patients and increased it in 6 patients. To summarize, dipyridamole showed adverse effects (aggravating effects on the ST change and/or on the threshold for angina pectoris) in 6 patients, beneficial effects in 8 and no effect in 4. A usual oral dose of dipyridamole induced myocardial ischemia during exercise in some patients while it improved it in a similar number of patients.

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Reduction of Myocardial Ischemia During Percutaneous Transluminal Coronary Angioplasty with Oxygenated Fluosol®

Kenneth M. Kent, Michael W. Cleman, Michael J. Cowley, Mervyn B. Forman, C. Carl Jaffe, Marvin Kaplan, Spencer B. King III, Mitchell W. Krucoff, Thomas Lassar, Bruce McAuley, Rafael Smith, Charlene Wisdom, and Daniel Wohlgeleit

Effects of a perfluorochemical emulsion (Fluosol®) on myocardial ischemia during percutaneous transluminal coronary angioplasty were examined in a multicenter trial of 245 patients. Severe anginal pain occurred less frequently in patients receiving Fluosol perfusion (21%) than routine angioplasty (34%) ($p < 0.05$). ST-segment changes at balloon deflation occurred significantly more in routine patients than in those receiving Fluosol perfusion (2.2 ± 1.2 vs 1.7 ± 0.9 mm; $p < 0.03$). Regional wall dysfunction (-561 ± 224 U) observed in routine angioplasty patients was not seen in patients receiving oxygenated Fluosol perfusion. Left ventricular ejection fraction was preserved at baseline levels during balloon inflation in patients perfused with oxygenated Fluosol but decreased significantly ($p < 0.001$) during occlusion in routine angioplasty patients. Thus, perfusion with Fluosol is effective in alleviating myocardial ischemia during angioplasty and can be safely administered in this patient population.

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Outcome Following Emergency Coronary Artery Bypass Grafting for Failed Elective Balloon Coronary Angioplasty in Patients with Prior Coronary Bypass

Joel K. Kahn, Barry D. Rutherford, David R. McConahay, Warren L. Johnson, Lee V. Giorgi, Thomas M. Shimshak, and Geoffrey O. Hartzler

The frequency and outcome of emergency coronary artery bypass grafting (CABG) for failed angioplasty in patients with prior CABG were assessed in 2,136 elective angioplasty procedures in prior CABG patients. Emergency CABG was required in 19 patients (0.9%) with prior CABG, compared with 130 of 6,974 patients (1.9%) without prior CABG ($p = 0.001$). Severe hemodynamic instability after acute closure required the placement of an intraaortic balloon pump in 3 patients, including 2 who required cardiopulmonary resuscitation. Three patients with high-risk features could not be weaned from cardiopulmonary bypass. The remaining 16 patients were discharged after a mean hospital stay of 16 days. Four patients developed new Q waves after CABG. At follow-up (mean 52 months, range 3 to 99), 1 patient died from a late acute myocardial infarction. The 15 survivors had no or mild angina and were free of further CABG. Thus, emergency CABG after failed angioplasty in patients with

Continued on page A22

ACTIVASE[®]

ALTEPLASE, RECOMBINANT

A TISSUE PLASMINOGEN ACTIVATOR

Brief Summary

Consult full prescribing information before using.

INDICATIONS AND USAGE: ACTIVASE[®] is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms.

ACTIVASE[®] is also indicated in the management of acute massive pulmonary embolism (PE) in adults: for the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs, and for the lysis of pulmonary emboli accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures. The diagnosis should be confirmed by objective means, such as pulmonary angiography or noninvasive procedures such as lung scanning.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE[®] is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • Severe uncontrolled hypertension.

WARNINGS: Bleeding The most common complication encountered during ACTIVASE[®] therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE[®] had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE[®] therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites of catheter insertion, arterial and venous puncture, cutdown and needle puncture).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE[®]. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE[®], it is preferable to use an upper extremity vessel accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE[®] and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with ACTIVASE[®] should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of ACTIVASE[®] therapy may be increased and should be weighed against the anticipated benefits: • Recent (within 10 days) major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent (within 10 days) gastrointestinal or genitourinary bleeding • Recent (within 10 days) trauma • Hypertension: systolic BP \geq 180 mm Hg and/or diastolic BP \geq 110 mm Hg • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or renal disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously infected site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants • Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias are not different from those often seen in the ordinary course of AMI and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTIVASE[®] are administered.

Pulmonary Embolism It should be recognized that the treatment of pulmonary embolism with ACTIVASE[®], Alteplase, has not been shown to constitute adequate clinical treatment of underlying deep vein thrombosis. Furthermore, the possible risk of reembolization due to the lysis of underlying deep venous thrombi should be considered.

RECAUTIONS: General Standard management of myocardial infarction or pulmonary embolism should be implemented concomitantly with ACTIVASE[®] treatment. Noncompressible arterial puncture must be avoided. Arterial and venous punctures should be minimized. In the event of serious bleeding, ACTIVASE[®] and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Immunogenicity There is no experience with readministration of ACTIVASE[®] if anaphylactoid reaction occurs, infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of ACTIVASE[®] has not been documented, readministration should be undertaken with caution.

Laboratory Tests During ACTIVASE[®] therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. ACTIVASE[®] is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE[®] with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function such as acetylsalicylic acid, dipyridamole may increase the risk of bleeding if administered prior to, during or after ACTIVASE[®] therapy.

Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE[®] to reduce the risk of rethrombosis. Because either heparin or ACTIVASE[®] alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE[®]. It is also not known whether ACTIVASE[®] can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE[®] should be given to a pregnant woman only if clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE[®] in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE[®] and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE[®] is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE[®] is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE[®] is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as >250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose \leq 100 mg	Total Dose $>$ 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	$<1\%$
retroperitoneal	$<1\%$	$<1\%$
epistaxis	$<1\%$	$<1\%$
gingival	$<1\%$	$<1\%$

The incidence of intracranial bleeding in patients treated with ACTIVASE[®], Alteplase, recombinant, is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-14 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE[®] should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials¹⁻⁷ is not significantly different in the ACTIVASE[®] treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively) ($p = 0.26$).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE[®] therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE[®] therapy. Therefore, ACTIVASE[®] therapy requires careful attention to potential bleeding site.

Allergic Reactions No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE[®] therapy.

DOSAGE AND ADMINISTRATION: ACTIVASE[®] is for intravenous administration only. **ACUTE MYOCARDIAL INFARCTION:** Administer ACTIVASE[®] as soon as possible after the onset of symptoms.

The recommended dose is 100 mg administered as 60 mg (34.5 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.⁸

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE[®] has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

PULMONARY EMBOLISM: The recommended dose is 100 mg administered by intravenous infusion over two hours. Heparin therapy should be instituted or reinstated near the end of or immediately following the ACTIVASE[®] infusion when the partial thromboplastin time or thrombin time returns to twice normal or less.

A DOSE OF 150 MG OF ACTIVASE[®] SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE[®] should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE[®] be reconstituted only with Sterile Water for Injection, USP without preservatives. Do not use Bacteriostatic Water for Injection USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE[®] 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because ACTIVASE[®] contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution in container permit.

ACTIVASE[®] may be administered as reconstituted at 1.0 mg/mL. As an alternative, the reconstituted solution may be diluted further immediately before administration in an equal volume of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to yield a concentration of 0.5 mg/mL. Either polyvinyl chloride bags or glass bottles are acceptable. ACTIVASE[®] is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

No other medication should be added to infusion solutions containing ACTIVASE[®]. Any unused infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE[®] is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vial containing vacuum, each packaged with diluent for reconstitution.

Storage: Store lyophilized ACTIVASE[®] at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

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prior CABG is required infrequently. In patients without extreme high-risk features, emergency repeat CABG can be accomplished with good hospital and long-term results.

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Role of Tricuspid Regurgitation and Left Ventricular Damage in the Treatment of Right Ventricular Infarction-Induced Low Cardiac Output Syndrome

Jean-François Dhainaut, Emmanuel Ghannad, Didier Villemant, Fabrice Brunet, Jean-Yves Devaux, Bruno Schremmer, Pierre Squara, Simon Weber, and Julien-François Monsallier

The effect of tricuspid regurgitation and extensive left ventricular infarction and its influence on the treatment response were studied in 20 patients with right ventricular myocardial infarction, 5 of whom had severe tricuspid regurgitation and 8 of whom had depressed left ventricular function. Volume loading increased cardiac output slightly in all patients. No treatment was effective in reestablishing an adequate hemodynamic status in those with severe tricuspid regurgitation; increasing right ventricular contractility with dobutamine failed to improve the forward stroke volume because of an increased regurgitant fraction. Dobutamine, which improved right ventricular function and consequently left ventricular preload, was especially efficacious in patients with depressed left ventricular function.

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The Divergent Recovery of ST-Segment Depression and Radionuclide Angiographic Indicators of Myocardial Ischemia

Pierce J. Vatterott, Peter C. Hanley, Harold T. Mankin, and Raymond J. Gibbons

The recovery after exercise of both electrocardiographic ST-segment depression and exercise-induced abnormalities in regional wall motion and ejection fraction was evaluated in 31 patients who had persistent ST-segment depression after exercise. In 27 (87%) of the 31 patients, abnormalities in wall motion and ejection fraction recovered more quickly than abnormalities in the exercise electrocardiogram. Only 15 of the 31 patients had persistent abnormalities in wall motion or ejection fraction after exercise, despite their persistent ST-segment depression. Compared with the 16 patients without such findings, these 15 patients had a worse wall motion score at peak exercise. Radionuclide angiographic evidence of ischemia recovers more quickly after exercise than ST-segment depression.

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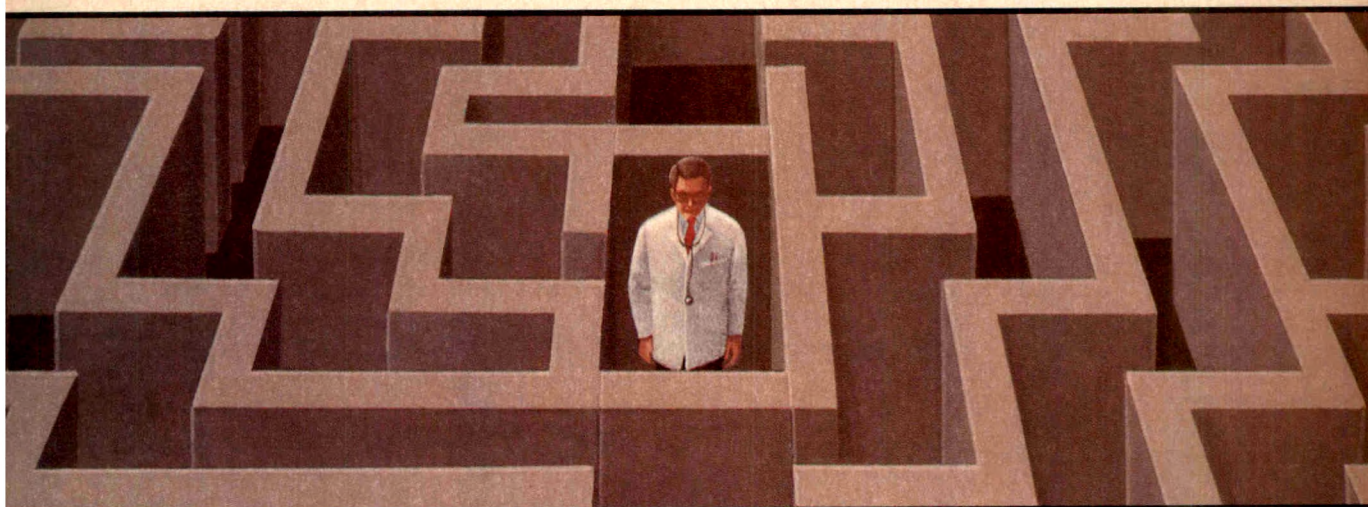
Acute Coronary Vasomotor Effects of Nifedipine and Therapeutic Correlates in Syndrome X

Piero Montorsi, Sergio Cozzi, Alessandro Loaldi, Franco Fabbicchi, Alvise Polese, Nicoletta De Cesare, and Maurizio D. Guazzi

In 18 patients with syndrome X, 10 mg sublingual nifedipine significantly increased coronary artery diameter, blood flow and plasma norepinephrine concentration and decreased coronary resistance and ST-segment

Continued on page A24

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a challenging dilemma



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response to exercise. Changes in blood flow showed a positive correlation with changes in lumen diameter, ST reaction to exercise and an inverse correlation with norepinephrine plasma levels. In a few patients, nifedipine did not modify or even worsened the effort test; in these cases blood flow was unchanged or decreased and norepinephrine plasma values modestly or greatly increased, respectively. After 4 weeks of treatment with nifedipine (10 to 20 mg, 4 times daily), the ST-segment response to exercise was further improved concomitantly with a decrease in norepinephrine plasma concentrations. Thus, nifedipine exerts a beneficial effect in syndrome X through coronary vasodilatation; reflex activation of the adrenergic system may, in some cases, restrict the therapeutic effect of the drug in the short-term but not in the long-term treatment.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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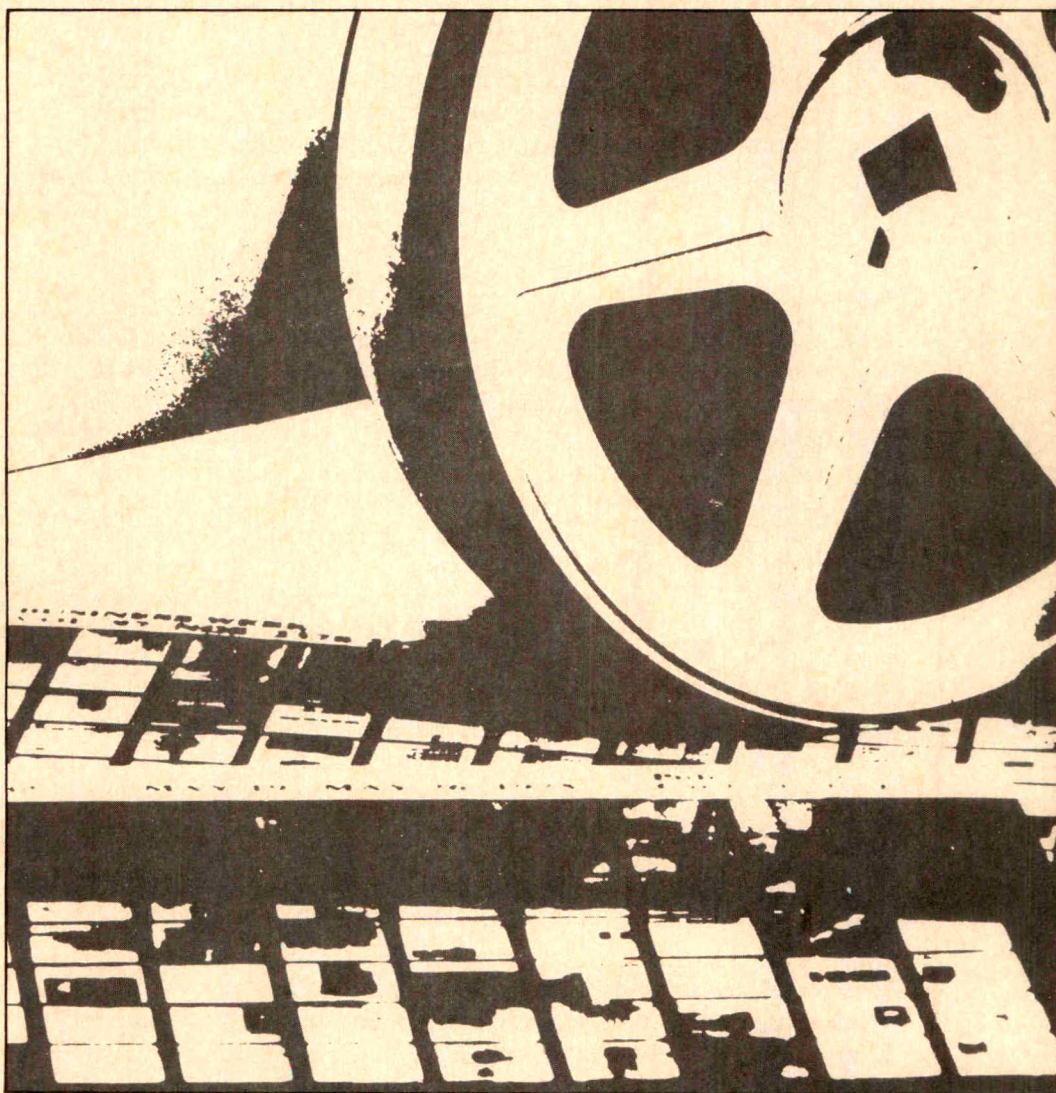
Relation Between Ventricular Late Endocardial Activity During Intraoperative Mapping and Low-Amplitude Signals Within the Terminal QRS Complex on the Signal-Averaged Surface Electrocardiogram

Hans-Joachim Schwarzmaier, Ulrich Karbenn, Martin Borggrefe, Jörg Ostermeyer, and Günter Breithardt with the technical assistance of Klaus Balkenhoff

Signal-averaged electrocardiogram (ECG) (3 algorithms) and intraoperative endocardial mapping at 36 sites were performed in 24 patients with ventricular aneurysm and drug-resistant sustained monomorphic ventricular tachycardia. In patients with a late potential, delayed local activation (>40 ms beyond the QRS complex in the intraoperative surface ECG) was recorded at 5.5, 5.5 and 5.6 of 36 endocardial sites. In patients without a late potential this type of endocardial delay was detected at 2.4, 1.1 and 0.9 sites, respectively ($p < 0.05$, $p < 0.01$, $p < 0.002$). The mean duration of endocardial delayed activity was 38, 35 and 37 ms in patients with a late potential versus 20, 19 and 11 ms in patients without ($p < 0.05$, $p < 0.05$, $p < 0.002$). However, there was no correlation between the amplitude or duration of a late potential and the number of sites exhibiting endocardial delayed activity ($r = -0.23$, $r = -0.05$, $r = 0.21$; correlation not significant for each) or the mean duration of the endocardial delay ($r = -0.25$, $r = -0.14$, $r = -0.07$, correlation not significant for each). Thus, the presence of a late potential, if present, is related to the mean duration of endocardial late activity as well as to the number of sites exhibiting delayed activity, and therefore is dependent on the mass of tissue activated with a given delay. However, neither the measured amplitude nor the duration allows a direct conclusion to parameters of endocardial delayed activity.

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CONGESTIVE HEART FAILURE

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Studies of Left Ventricular Dysfunction (SOLVD)—Rationale, Design and Methods: Two Trials That Evaluate the Effect of Enalapril in Patients with Reduced Ejection Fraction

The SOLVD Investigators

The Studies of Left Ventricular Dysfunction is an integrated research program of patients with low ejection fraction or congestive heart failure. The program includes 2 clinical trials, 1 in symptomatic and 1 in asymptomatic patients, of the effectiveness of enalapril on mortality. In addition, a registry of patients with left ventricular dysfunction has been established.

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Radial Arterial Pressure Measurements May Be a Poor Guide to the Beneficial Effects of Nitroprusside on Left Ventricular Systolic Pressure in Congestive Heart Failure

Gerald J. Simkus and David H. Fitchett

The effect of nitroprusside on central aortic and peripheral radial arterial pressures was studied in 10 patients with severe cardiac failure. When a late systolic aortic pressure peak was present, nitroprusside reduced aortic more than radial systolic pressure. As a result the difference between aortic and radial systolic arterial pressures increased during nitroprusside: control 13 ± 4 mm Hg, nitroprusside 20 ± 6 mm Hg ($p < 0.025$). In the absence of an aortic late systolic pressure peak, the aortic radial systolic pressure difference was unchanged. These results show that a reduction of radial arterial systolic pressure by nitroprusside may underestimate the true reduction of aortic and hence left ventricular systolic pressure.

VALVULAR HEART DISEASE

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Early and Late Changes in Left Ventricular Systolic Performance After Percutaneous Aortic Balloon Valvuloplasty

David H. Harpole, Charles J. Davidson, Thomas N. Skelton, Katherine B. Kisslo, Robert H. Jones, and Thomas M. Bashore

Seventeen patients underwent first-pass radionuclide angiocardiology with simultaneous high-fidelity micromanometer pressure before, 10 minutes after and 6 months after aortic valvuloplasty. Immediately after the procedure, the mean and peak aortic transvalvular gradient decreased and aortic valve area increased. Using echocardiography, meridional and sys-

Continued on page A33

tolic wall stress decreased. Left ventricular ejection fraction increased and end-diastolic volume and end-diastolic pressure both decreased. Left ventricular stroke work, as derived from the area of the pressure-volume loop, also decreased as the loop shifted to the left and downward. At the 6-month study, restenosis occurred in most patients but was not always accompanied by a worsening of clinical status. The pressure volume loop shifted back toward baseline and the ejection fraction decreased as end-systolic stress increased. There were little data to support an intrinsic change in myocardial contractile performance at any postprocedural interval after aortic valvuloplasty. Rather, the changes in hemodynamics observed could be explained solely by altered loading conditions.

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Detection and Assessment of Severity of Tricuspid Regurgitation Using First-Pass Radionuclide Angiography and Comparison with Pulsed Doppler Echocardiography

Kim A. Williams, Patricia E. Walley, and James W. Ryan

Noninvasive detection and semiquantitative assessment of tricuspid regurgitation (TR) were performed in this study using first-pass radionuclide angiography (RNA). The percentage of tracer entering the right atrium during right ventricular systole was quantitated as the right atrial "injection fraction." The results were compared with semiquantitative Doppler echocardiographic estimation of TR severity in 51 patients. There were 27 patients with no evidence of TR by Doppler; 26 were also negative by RNA. All 24 patients with TR by Doppler had a positive right atrial injection fraction. Comparison of right atrial injection fraction grade ranges with semiquantitative grades of TR severity on Doppler revealed identical grades in 21 of the 24 patients, with a 1 grade difference in the remaining 3 patients. Thus, right atrial "injection fraction" quantitation during first-pass RNA allows detection and grading of the severity of TR, with results very similar to pulsed Doppler echocardiography.

CONGENITAL HEART DISEASE

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Long Follow-Up (to 43 Years) of Ventricular Septal Defect with Audible Aortic Regurgitation

Larry A. Rhodes, John F. Keane, John P. Keane, Kenneth E. Fellows, Richard A. Jonas, Aldo R. Castaneda, and Alexander S. Nadas

From 1946 to March 1989, 92 patients (33 women and 59 men) were seen with ventricular septal defect (VSD) and audible aortic regurgitation (AR). The VSD was subcrystal in 62 patients and subpulmonary in 21. The median age of onset of AR was 5.3 years. The risk of developing AR was 2.5 times greater in those with a subpulmonary VSD. The aortic valve was tricuspid in 90% and bicuspid in 10%. The incidence of infective endocarditis was 15.4 episodes/1,000 patient years. Twenty patients were followed medically, equaling some 297 patient years. In the 72 patients operated on, there were 15 perioperative and 5 late deaths. Procedures

Continued on page A34

consisted of VSD closure alone in 7 patients, VSD closure and valvuloplasty in 50 and VSD closure and aortic valve replacement in 15. The degree of AR was more effectively decreased by valvuloplasty in those operated on under the age of 10.

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Frequency and Prognosis of Arrhythmias After Operative "Correction" of Tetralogy of Fallot

Guy Vaksman, Anne Fournier, André Davignon, Gilles Ducharme, Lucile Houyel, and Jean-Claude Fouron

Two hundred twenty-four consecutive patients operated on for tetralogy of Fallot were followed from 1 to 28 years (mean 11). Mean age at surgery was 5.3 years (range 1 to 14). Postoperative right ventricular systolic pressure was >60 mm Hg in 19 of 213 patients (9%). Twenty-four-hour ambulatory monitoring in 92 patients demonstrated significant ventricular arrhythmias (\geq grade 2 of the Lown grading system) in 41 (45%). Incidence of ventricular arrhythmias correlated with length of follow-up and duration of cardiopulmonary bypass. No correlation was found with age at surgery, postoperative right ventricular systolic pressure and importance of conduction defects on electrocardiogram. There were no sudden deaths during follow-up. Thus, systematic treatment of postoperative ventricular arrhythmias in tetralogy of Fallot should be reconsidered.

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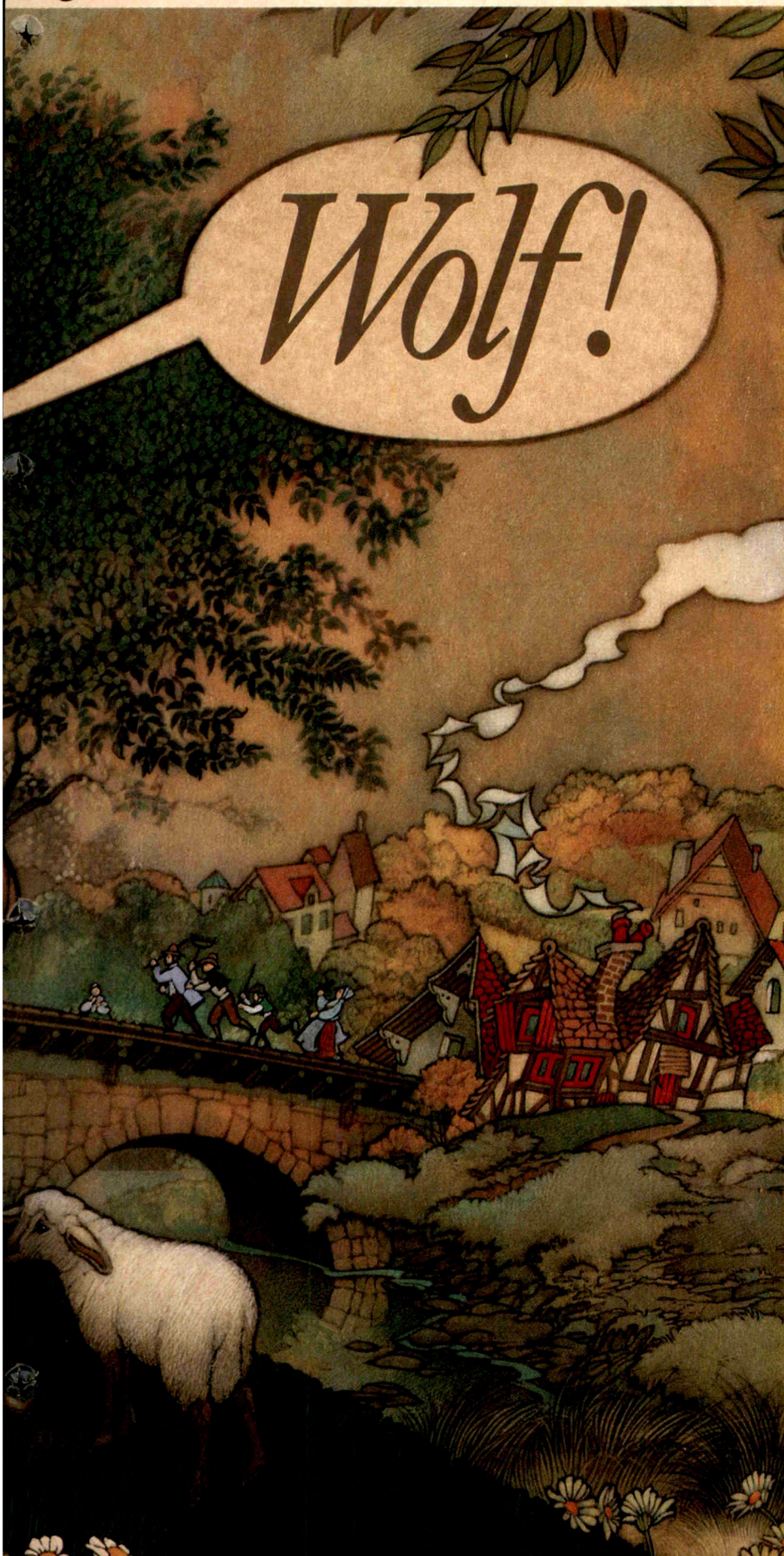
An Electrocardiographic Midterm Follow-Up Study After Anatomic Repair of Transposition of the Great Arteries

Juan Villafane, Sara White, Francisco Elbl, Allan Rees, and Robert Solinger

Twenty-four neonates had 170 electrocardiograms and fifty-three 24-hour electrocardiograms after anatomic repair for simple transposition of the great arteries. These tracings were assessed for rhythm and conduction abnormalities. Three patients had atrial or ventricular premature complexes detected before surgery. Electrocardiographic abnormalities found after surgery were transient ST and T changes in 7 patients, right bundle branch block in 1 patient, left bundle branch block in 2 patients, transient second-degree atrioventricular block in 1 patient and a qS pattern in V_6 in 1 patient. A normal P-R interval and P-wave axis were present in all but 1 patient. Asymptomatic low-grade atrial and ventricular ectopic activity was infrequently observed in 24-hour electrocardiograms performed 1, 2, 3 and 4 years after surgery. After a mean follow-up of 3 years, all of our patients remain in sinus rhythm.

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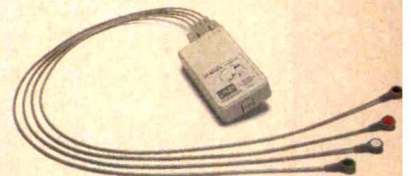
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MISCELLANEOUS

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Safety of Cardiac Angiography with Conventional Ionic Contrast Agents

John W. Hirshfeld, Jr., William G. Kussmaul, Peter M. DiBattiste, and the Investigators of the Philadelphia Area Contrast Agent Study

We gathered data describing the frequency of adverse reactions to conventional ionic angiographic contrast agents in 4,630 cardiac angiographic procedures. The adverse reaction rate was 14.2% for minor and 1.3% for major events. There were no deaths. Adverse reactions were more frequent in patients with higher New York Heart Association class symptomatology and with elevated left ventricular end-diastolic pressure. The adverse reaction rate was not increased in patients with more extensive coronary artery disease, reduced left ventricular ejection fraction or reduced cardiac index. The overall adverse reaction rate was probably influenced favorably by physician behavior. Six percent of procedures were abbreviated either because of an adverse reaction or concern that a reaction might occur if the procedure were continued. The diagnostic data obtained were judged to be inadequate in 0.8% of the procedures. With appropriate operator caution, cardiac angiography can be performed safely in most patients with conventional ionic contrast agents.

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Self-Efficacy and In-Patient Cardiac Rehabilitation

Neil B. Oldridge and Barbara L. Rogowski

We assessed changes in self-efficacy in 51 cardiac patients after randomization to either a ward ambulation program or a dedicated exercise center before hospital discharge. There were no differences between the groups in self-efficacy at baseline, the time of hospital discharge or 7 days later. Significant improvements in self-efficacy scores were observed by day 28 in both groups for routine physical activities and daily living tasks with the exercise center patients demonstrating higher self-efficacy scores only for walking time ($p = 0.041$) and overall exertion ($p = 0.024$). We conclude that, for most of the self-efficacy variables considered, the 2 in-patient exercise programs are equally effective in improving self-efficacy scores for physical activities and daily living tasks over the first 28 days after return to home. The lower costs associated with ward ambulation programs suggest that they are more cost-effective.

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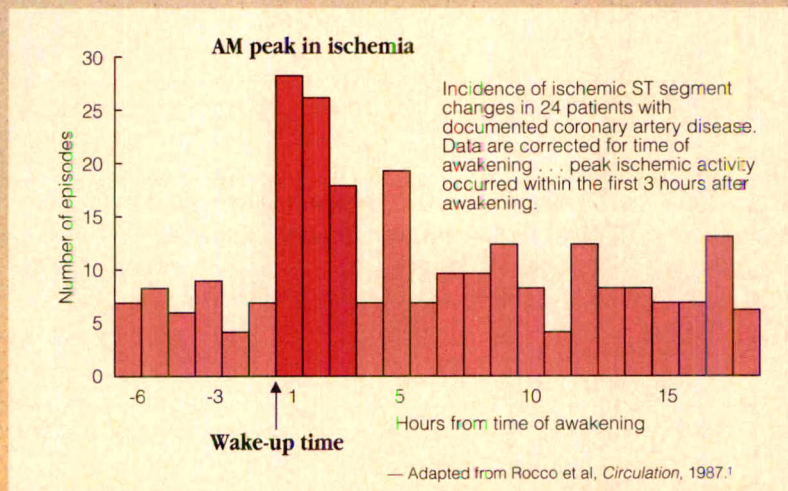
Late Morphologic Findings After Coronary Endarterectomy

V.M. Walley, R.W. Byard, and W.J. Keon

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Plasma Norepinephrine and Treatment of Heart Failure

Gregory J. Hasking , Murray D. Esler and Garry L. Jennings

**Usefulness of Echocardiography in Managing Left Ventricular
Thrombi After Acute Myocardial Infarction**

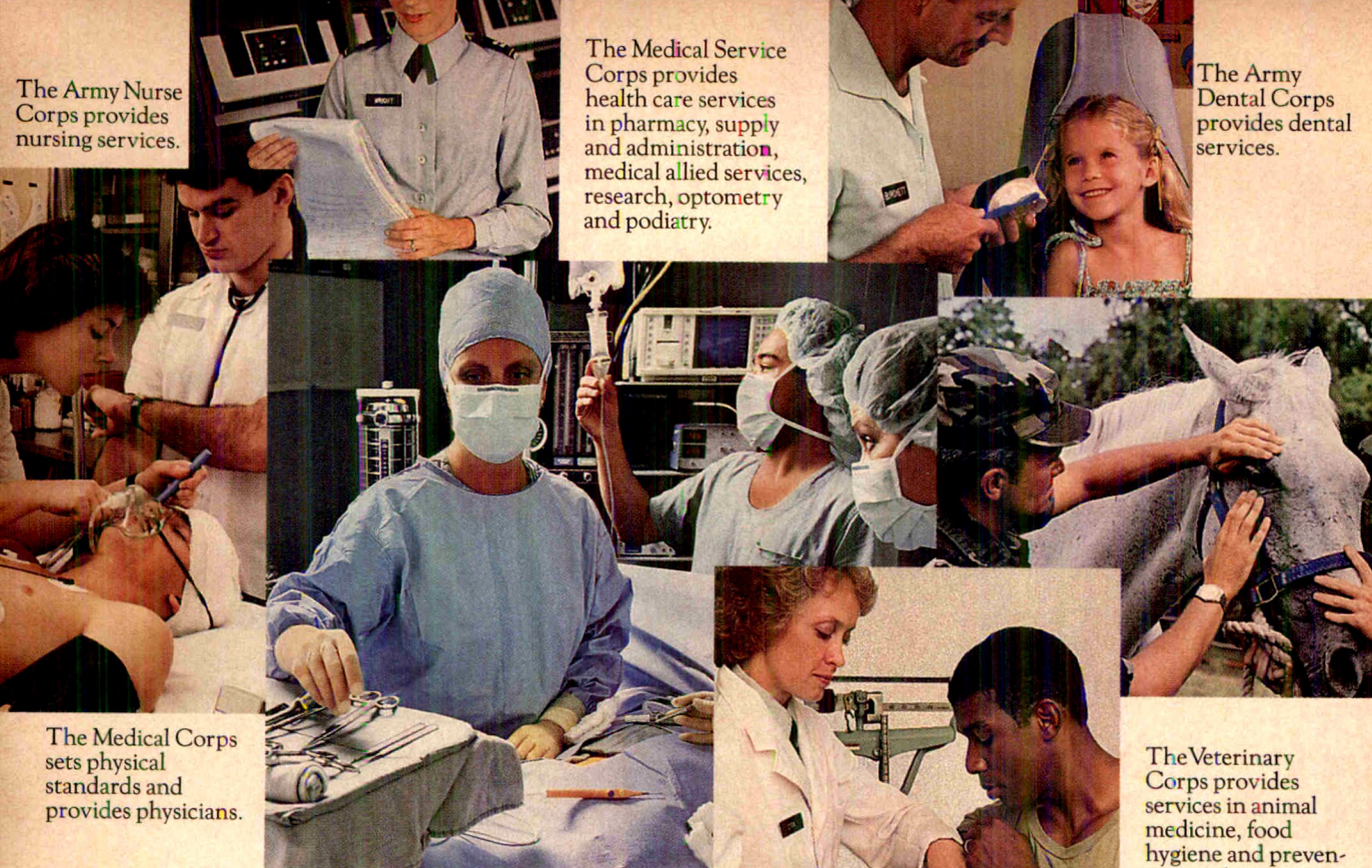
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Secondary Prevention After High-Risk Acute Myocardial Infarction with Low-Dose Acebutolol

Jean-Pierre Boissel, MD, Alain Leizorovicz, MD, Hélène Picolet, MD, and Jean-Claude Peyrieux, PhD, for the APSI Investigators*

Acebutolol et Prévention Secondaire de l'Infarctus (APSI), a randomized, placebo-controlled trial, was designed to test long-term acebutolol, 200 mg twice daily, a β blocker with mild intrinsic sympathomimetic activity, in the prevention of late death in high-risk postacute myocardial infarction (AMI) patients. APSI was planned because patients with a death rate $>20\%$ have not been enrolled in significant numbers in previous trials and in such high-risk patients, it remained to be proven that β blockers have a beneficial effect. Patients with an expected average risk of $>20\%$ were to be selected based on clinical criteria. At the time of the second interim analysis, the placebo group 1-year mortality was much lower than expected (12%). The ethical board recommended to stop the trial: 309 patients had been allocated to placebo, 298 to acebutolol. The average delay between onset of symptoms and inclusion was 10.5 days. The average follow-up was 318 days after inclusion. About the same number of patients were discontinued from study treatment in both groups. All patients were included in the analysis. There were 17 deaths in the acebutolol group and 34 in the placebo group, a 48% decrease ($p = 0.019$). The vascular mortality decreased by 58% ($p = 0.006$), the highest ever observed with a β blocker. All cardiovascular causes of death, including congestive heart failure, were less frequent in the acebutolol group. Although the objective was not achieved, APSI patients were at a higher risk than the average of the 9 previous trials with β blockers (12% instead of 7%). In addition, the total mortality reduction did not decrease in 9 subgroups with increasing mortality risk from 2 to 23%. APSI shows that moderately severe postAMI patients can benefit from a β -blocking treatment and a β -blocker with mild intrinsic sympathomimetic activity can be effective.

(Am J Cardiol 1990;66:251-260)

From the APSI Coordinating Center, Unité de Pharmacologie Clinique, Lyon, France. Manuscript received January 2, 1990; revised manuscript received and accepted April 3, 1990.

Address for reprints: APSI Coordinating Center, Unité de Pharmacologie Clinique, 162, Avenue Lacassagne—69424 Lyon Cedex 3.

*See Appendix.

Acebutolol et Prévention Secondaire de l'Infarctus (APSI) was a randomized, placebo-controlled trial of acebutolol, a β blocker with moderate intrinsic sympathomimetic activity in the prevention of late death in high-risk patients surviving an acute myocardial infarction (AMI). The long-term effect of late intervention (>24 hours from onset) with β -blocker treatment on survival in postAMI patients has been assessed in several trials over the past 15 years.¹⁻¹² Some trial results were statistically significant on their own. Most, however, were not. Several metaanalyses concluded that β -blocking treatment was beneficial in patients who had survived an AMI. The relative decrease of 1-year mortality was about 25%.^{13,14,15} A metaanalysis conducted in adding the 2 more recently reported trials^{11,12} gives similar results. The average 1-year mortality on the placebo groups of the first 9 trials was 7.2%, whereas in a nonselected cohort of patients who have survived ≥ 7 days after an AMI, it was 17%.¹⁶ Adding the 2 more recent trials does not change this observation. However, 2 trials were designed to enroll only "high-risk" patients.^{3,7} The 1-year mortality in their placebo groups was 12 and 13%; in 1, the death rate in the verum group was higher³ and in the other the gain was not statistically significant.⁷ Thus, evidence supporting the benefit from treating postAMI patients with β -blockers came from low- to moderate-risk cohorts.

A posthoc subgroup analysis of the pooled data from the first 9 trials showed that subgroups of patients with a higher than average risk of dying were those who benefitted the most from the treatment.¹⁵ Even in these subgroups, the 1-year placebo group mortality was $<17\%$ with the exception of the subgroup of patients who received digitalis before entry whose mortality was 18.8%. This subgroup represented $<7\%$ of the total number of patients (13,679). Hence, the question remained open whether high-risk patients who represent most of the target population benefit from β -blocking treatment.

The Clinical Pharmacology and Therapeutic Working Group of the French Society of Cardiology decided to initiate a randomized trial of β -blocking treatment in patients with a risk of dying during the first year after an AMI of $\geq 20\%$. The rationale, the objectives and especially the placebo control have been accepted independently by both the Ethics Committee of the Claude Bernard University and the Ethics Committee of the French Society of Cardiology.

TABLE I Baseline Characteristics

	Patients Screened in the 7 Centers		Total No. of Patients Included (n = 607)
	Not Included (n = 1664)	Included (n = 219)	
Men	75.8	77.1	72.9
Mean age (yrs)	62.9	61.1	62.9
Prior history			
Angina pectoris	37.9	37.8	41.5
Angina pectoris >5 yrs	34.9	30.6	19.3
Unstable angina	53.9	55.0	28.9
Documented AMI	18.0	24.8	23.3
Congestive heart failure	17.0	27.5	27.1
Acute pulmonary edema	13.6	4.8	4.9
Nocturnal dyspnea	12.8	4.8	7.3
Severe exertional dyspnea	91.1	98.4	95.1
Dyspnea on flat ground	42.4	37.1	42.7
Valvular disease	4.3	3.7	4.5
Intermittent claudication	10.3	8.7	8.8
Renal failure	3.3	1.8	3.6
Diabetes mellitus	12.1	17.5	14.6
Liver cirrhosis	2.4	2.8	1.7
Risk factors			
Cigarette smoker (actual or past)	65.5	72.9	65.5
Systemic hypertension	25.9	26.6	32.9
Onset of symptoms			
Shock	4.9	6.0	5.0
Palpitations	2.6	3.7	5.3
Acute pulmonary edema	10.2	11.5	9.8
Proven conduction or rhythm disturbance	4.8	9.7	7.3
Atrial flutter or fibrillation	6.9	11.5	13.5
Ventricular flutter or fibrillation	3.2	4.6	5.0
At admission			
Arrhythmia	18.0	21.5	10.1
Murmur	53.7	35.4	15.2
Cyanosis	2.9	1.8	3.6
Hepatomegaly	3.9	3.7	2.8
Hepatojugular reflux	7.0	8.3	6.4
Cold hands and feet	7.1	10.1	5.0
Median no. of secondary risk factors	5	8	8

AMI = acute myocardial infarction.

METHODS

Selection of high-risk patients, eligibility and follow-up: Selection of high-risk patients for inclusion in the trial was based on an algorithm set-up from the Essai de Prévention Secondaire de l'Infarctus du Myocarde registry.¹⁶ Materials and methods used for constructing this algorithm have been presented previously.¹⁷ In brief, it consists of counting the number of so-called secondary risk factors presented by every patient considered for entry. Simulation of the selection with this algorithm on the Essai de Prévention Secondaire de l'Infarctus du Myocarde registry identified 49% of the total population with an average 1-year mortality of 26%.

Patients were eligible in the following cases: if they had ≥ 2 of the 3 classic signs of AMI, that is, typical chest pain of ≥ 1 hour in duration, typical Q waves and significant release of cardiac enzyme(s); if they were admitted for this acute event >2 and <22 days before; and if they presented ≥ 6 of the secondary risk factors of the selection algorithm, including ≥ 1 "major" secondary risk factor (i.e., before documented AMI, history of dyspnea when walking on flat ground, documented atrial fibrillation, ventricular fibrillation, ventricular

tachycardia, overt heart failure or sinus tachycardia during the reference event, recurrent AMI or angina pectoris before the eighth day). Eligible patients were then checked for exclusion criteria, including transient exclusion criteria such as heart rate <45 beats/min, complete auriculoventricular block and acute heart failure that required treatment with ≥ 2 drugs of different classes (e.g., diuretics and vasodilators). If the condition disappeared before the twenty-second day, the patient could be included. Exclusion criteria were the following: contraindication to β -blocking treatment; noncardiac disease with poor prognosis; impossibility to participate; indication to β -blocking treatment; age >75 years; death; malignancy; valvular disease; coma; asthma; chronic bronchopneumopathy; Raynaud syndrome; participation in another study; and patients enrolled in APSI before. Once admitted in the trial, the patients were treated and followed-up for 1 year with quarterly visits in the outpatient clinic of the clinical centers. However, some patients were followed-up by their general practitioner or their cardiologist.

Random allocation to treatment: Central randomization was achieved with a Minitel®, a terminal linked to the telephone system allowing an on-line remote data

TABLE II Reasons for Noninclusion in 1,883 Patients Evaluated (719 Excluded During the First 48 Hours)

	No.	%
Enrolled in APSI before	5	0.7
Participation in other study	5	0.7
Impossibility	228	31.7
Malignancy	39	5.5
Valvular disease	31	4.4
Age >75 yrs	97	13.6
Indication to β blockers	128	18.0
Other contraindication to β blockers	131	18.4
Raynaud syndrome	10	1.4
Chronic bronchopneumopathy	51	7.1
Asthma	20	2.8
Nonproven infarction	57	8.0
Coma	13	1.8
Death	53	7.4

APSI = Acebutolol et Prévention Secondaire de l'Infarctus.

entry. Participating patients were randomized either to acebutolol 200 mg twice daily or to an identical placebo. Eligibility criteria were keyed by the investigator on a Minitel®. After editing of the eligibility criteria by the central computer, the treatment number was shown on the screen. Random permutations with blocks of 6 were used for randomization. Treatment numbers were not sequential.

Selected outcomes: The primary outcome was total death. Every death was documented and cause of death validated by the critical event committee. Cardiovascular death was the secondary outcome.

Treatments: Tablets of acebutolol and placebo were indistinguishable. The treatment started without delay after the computerized allocation of a treatment number. A round-the-clock telephone service was available for investigators who needed to know the treatment. The code could only be broken in case of life-threatening conditions, the care of which required to know the treatment given to the patient.

Acebutolol et Prévention Secondaire de l'Infarctus (APSI) registry: In order to check the adequacy of the trial sample to the target population in terms of risk at 1 year and to compare the selected patients with the non-included patients, a registry has been set up in 7 centers to register all patients admitted for an AMI throughout the trial. Baseline data, including reason(s) for non-inclusion, for all these patients were collected on the same study forms. Occurrence of death for the non-included patients was surveyed through administrative procedures.

Study organization: The study was organized as a prospective multicenter trial. The coordinating and data handling center was in charge of managing the trial, editing collected data, controlling compliance by both investigators and patients, randomizing the treatment through an on-line computerized procedure and analyzing the results. The Policy Board monitored the trial results on an ongoing basis. Its voting members were not otherwise involved in the trial and had no connection with the sponsor. Nobody but the voting members of this committee and 4 individuals in the coordinating center were aware of the interim results. The critical

TABLE III Baseline Characteristics: the 7 Comparisons that Led to a p Value ≤ 0.05

	Acebutolol		Placebo		p Value
	No.	%	No.	%	
Hypertriglyceridemia	18	6.1	6	1.9	0.009
Atrial fibrillation or flutter*	49	16.6	32	10.5	0.028
Heparin*	294	99.0	297	96.1	0.023
Antihypertensive therapies*	8	2.7	21	6.8	0.018
Pacemaker*	6	2.0	18	5.8	0.016
Asthenia†	143	49.1	167	55.1	0.036
Inotropics†	18	6.2	8	2.6	0.035

* First 48 hours; † From day 3 to day 21.

TABLE IV Cardiovascular Causes of Death

	Acebutolol	Placebo	Total
Sudden death	6	9	15
Fatal reinfarction	3	7	10
Heart failure	3	8	11
Rhythm disturbance	0	2	2
Other vascular death	0	4	4

Other vascular deaths were stroke, thrombosis, electromechanical dissociation and undefined vascular death.

TABLE V Reasons for Withdrawal from Study Treatment

	Acebutolol	Placebo	Total
Side effects	12	11	23
Indication to β blockers	12	27	39
Contraindication to β blockers	40	28	68
Other treatment contraindicated with β blockers	11	13	24
Patient or physician refusal	15	12	27
Others	12	18	30
Total	102 (33.0%)	109 (36.6%)	211 (34.8%)

events committee met periodically to classify the causes of death. Its members were not otherwise involved in the trial and were kept blind vis-à-vis the study treatment. Vascular death was defined as any death that could be related to a cardiovascular event, such as sudden death, myocardial infarction, cardiac failure, stroke or cerebral hemorrhage. There has been no attempt to identify nonfatal events not reported in regular study forms, that is, no notification procedure was set on during the trial. Hence, the frequencies of nonfatal clinical events are probably not fully accurate. A similar restriction applies to symptoms or signs noted during the follow-up.

Sample size: Accounting for an expected decrease of 40% of the 1-year mortality, a 95% power, a 5% significance level and a 20% average mortality in the control group, 1,080 patients were to be recruited.

Study monitoring: The policy board decided to monitor total mortality data with a 1-sided group sequential plan. Interim analyses were scheduled every 20 deaths. The global first kind statistical error risk was kept at 0.05. In addition, the policy board was in charge of monitoring the relevance of the study sample to the target population. Patient enrollment started in April

1987. At the time of the second interim analysis (40 deaths) in September 1988, 44 centers had recruited 555 patients with a mean follow-up of 271 days. Extrapolation of the death rate in the placebo group to 1 year showed a much lower than expected mortality of about 12%, instead of $\geq 20\%$. In addition, the proportion of enrolled patients was 12%, whereas about 30% was the expected figure. Moreover, from simulation with the registry of considered patients, it became clear that this percentage should have been 49%. The policy board recommended to stop the trial because they felt it was unethical to continue with a study population that was not markedly different from those of the previous trials. This recommendation was endorsed by the Steering Committee. Enrollment of patients was terminated on December 25th. When the recommendation to stop was made, there were 27 deaths in the placebo group and 13 in the acebutolol group. The corresponding p value of

the Logrank test of the 1-sided monitoring procedure was 0.014. Compared to 0.0035, the nominal level of significance for this test, it was not significant and the upper boundary was not crossed.

Analysis and statistical tests: The analysis for primary and secondary outcomes was performed on an intention to treat basis. All the results in this report come from the intention to treat approach. Chi-square or Fisher exact test was used to compare rates when a theoretical number was < 5 . Student's *t* test or analysis of variance was used to compare quantitative data. Cox regression was used to adjust the mortality rate difference to delay of survey and baseline variables. Mantel-Haenzel procedure was used to account for qualitative baseline variables. Comparison of APSI results with the 11 previous trials of β -blocking treatment in postAMI patients was done by conducting a metaanalysis of the 12 trials. Ninety-five percent confidence limits were

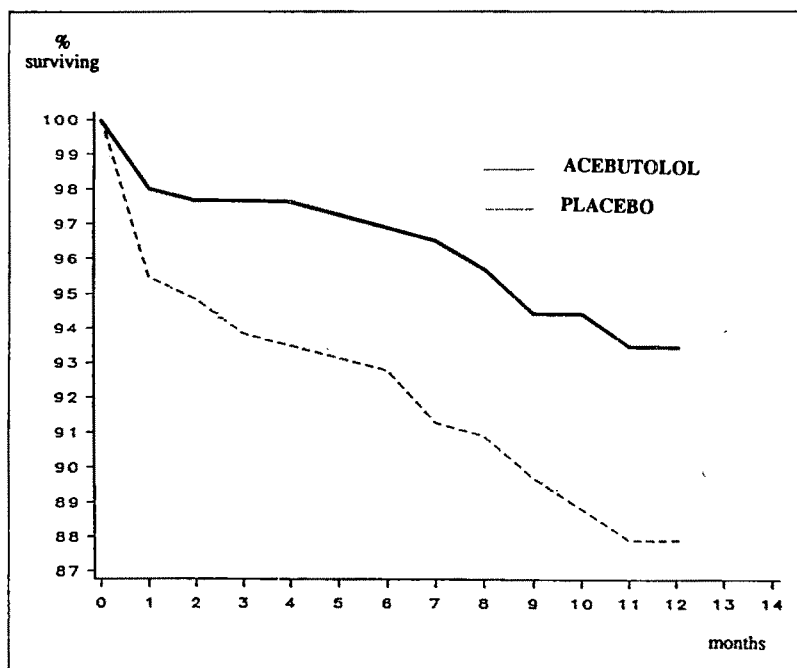


FIGURE 1. Actuarial survival curves.

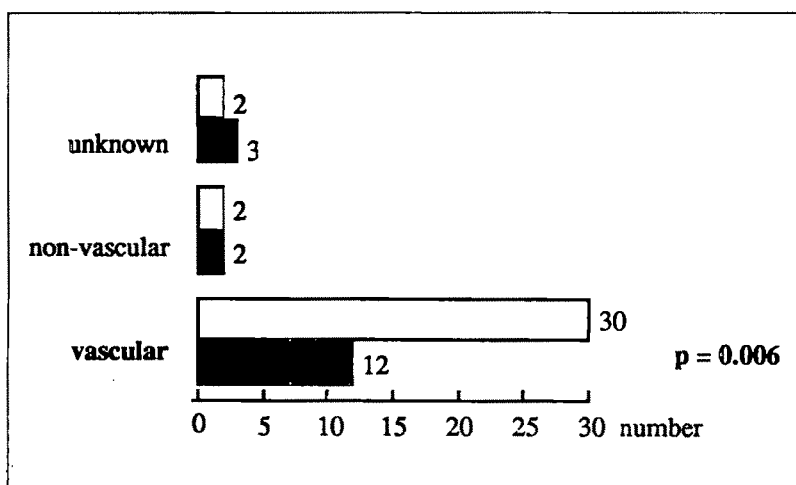


FIGURE 2. Causes of death.

computed for the odds ratios. Hence, the data from the 12 trials were compared with a common criterion. With 1,080 patients and a 12% 1-year mortality in the placebo group and a 6% 1-year mortality in the treated group, the expected number of interim analyses was 4. If the trial hadn't been stopped prematurely, the total number of analyses on mortality would not have exceeded 5. Hence, using the approximate rule derived from Tukey,¹⁸ the nominal level of significance for an overall level of 0.05 is $0.05/\sqrt{5} = 0.022$ (the original Tukey's rule would give 0.01; however, it assumes the interim analyses are independent and thus is overconservative). Thus, only p values <0.02 should be considered significant for the 2-sided tests. Ninety-five percent confidence limits were computed.

RESULTS

When the trial was stopped, 607 patients have been recruited by the 44 clinical centers (average 13.8 patients/center; minimum 1; maximum 43); 309 have been allocated to placebo, 298 to acebutolol. Their mean age was 62.9 years and 73% were men; 83.7% have had a transmural infarction. The electrocardiographic site of the infarct was anterior in 51% and infero-posterior in 40.6%. Other baseline characteristics are listed in Table I. In the 7 centers where the APSI registry has been kept throughout the recruitment, 1,883 patients were registered. Among them, 219 (11.6%) were eventually randomized. The most frequent reasons for noninclusion of eligible patients were alleged contraindication to β -blocking agents, indica-

FIGURE 3. Mortality decrease according to secondary risk factors. RR = risk ratio.

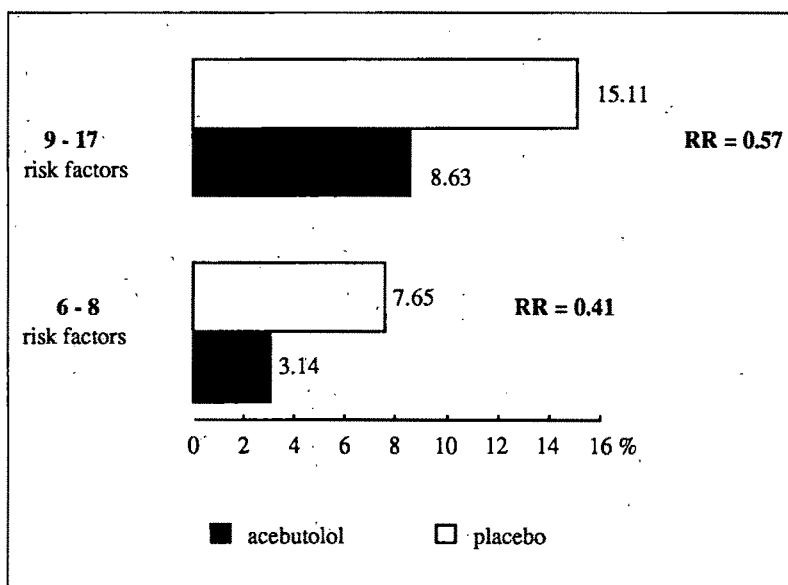


FIGURE 4. Actuarial curves of withdrawals from study treatment.

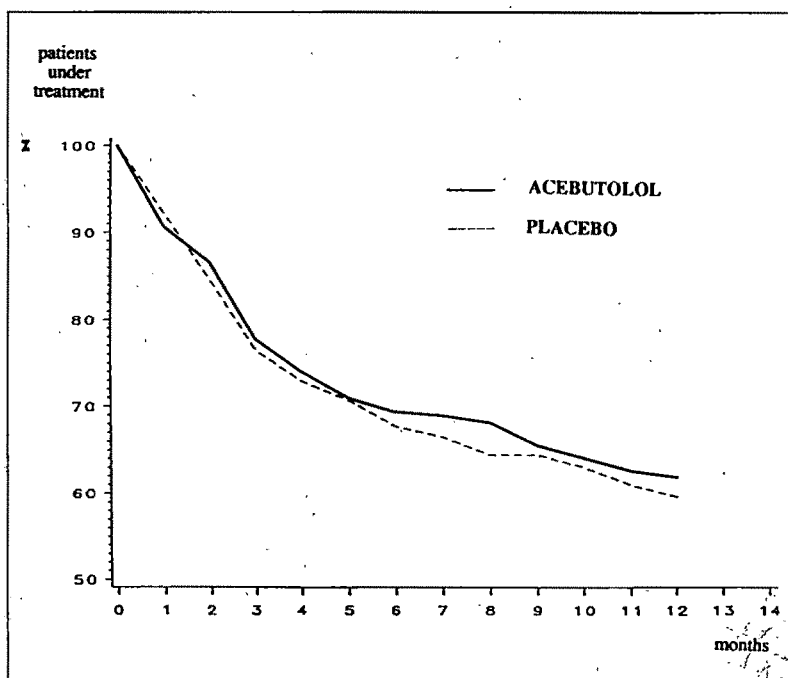


TABLE VI Serious Clinical Events

	Acebutolol		Placebo	
	No.	%	No.	%
Reinfarction	6	2.0	4	1.3
Fatal or nonfatal reinfarction	9	3.0	11	3.6
Acute pulmonary edema	20	6.7	15	4.9
Fatal or nonfatal cardiac failure	22	7.4	22	7.1
Ventricular flutter or ventricular fibrillation	1	0.3	0	0.0
Ventricular flutter, ventricular fibrillation or fatal arrhythmia	0	0.0	3	1.0
Other vascular events	35	11.7	28	9.1
Other nonvascular events	51	17.1	70	22.7

TABLE VII Symptoms or Signs Noted During Follow-Up

	Acebutolol		Placebo	
	No.	%	No.	%
Angina pectoris	98	32.9	92	29.8
Heart failure	137	46.0	105	34.0
Conduction or rhythm disturbance	102	34.2	101	32.7
Sinus bradycardia	48	16.1	16	5.2
Sinus tachycardia	8	2.7	26	8.4
Atrioventricular block	17	5.7	15	4.9
Right bundle branch	11	3.7	16	5.2
Left bundle branch	4	1.3	7	2.3
Flutter or atrial fibrillation	16	5.4	12	3.9
Extrasystola or ventricular tachycardia	16	5.4	26	8.4
Other arrhythmia	24	8.1	29	9.4

tions for such drugs and impossibility to participate (Table II). Overall included patients had more secondary risk factors than nonincluded patients (Table I). Application of the risk function based on the Essai de Prévention Secondaire de l'Infarctus du Myocarde registry^{16,17} gave a theoretical 1-year mortality for the 309 patients in the placebo group at 20.0%, whereas when applied to all the registered patients still alive at 10 days, the figure was 15.1%; the corresponding observed figures extrapolated to 1-year follow-up with the assumption of an exponential decay were 12.4 and 13.4%, respectively. None of the 607 included and randomized patients were lost-to-follow up for the main outcome. On a theoretical total number of study forms of 4,440, 1.9% were not received at the coordinating center; 7.7% of those received and continuously edited and corrected presented ≥ 1 error when the final analysis was done. Eighty-four percent of the scheduled follow-up visits were done. Twenty-one patients were not followed-up by the clinical centers where they were recruited as written in the protocol; instead they have been followed by their general practitioners or cardiologists.

The 2 groups were well balanced for the baseline characteristics of randomized patients; out of >266 comparisons of baseline data, only 7 led to p values <0.05 (Table III). This is well within random variations. The average delays between onset of symptoms and inclusion in the trial were 11.1 days in the acebutolol group (minimum 3; maximum 31) and 10.4 in the placebo group (minimum 2; maximum 29).

The average follow-up duration was 318.5 days after inclusion. The ratio effective/expected duration of fol-

low-up was 0.96 in the acebutolol group and 0.91 in the placebo group.

In regard to total mortality, there were 17 deaths in the acebutolol group (5.7%) and 34 in the placebo group (11%). This 48% decrease in total mortality leads to a 0.019 (2-sided) or 0.013 (1-sided) p value. The survival curves did not cross over (Figure 1). There were 30 vascular deaths in the placebo group (9.7%) and 12 in the acebutolol group (4.0%, Figure 2). This 58% decrease in vascular mortality leads to a p value of 0.006 (2-sided). All cardiovascular causes of death were less frequent in the acebutolol group (Table IV). The total mortality decrease did not appear to be correlated with the number of secondary risk factors (Figure 3). The homogeneity test for the 2 risk ratios, that is, 0.57 for patients with >8 secondary risk factors and 0.41 for those with 6 to 8 secondary risk factors, leads to a p value of 0.646. When the difference in total mortality is adjusted for 15 baseline characteristics (gender, age, baseline heart rate, diastolic and systolic blood pressures, interval MI/randomization, history of prior AMI, angina pectoris, congestive heart failure, hypertension, prior treatment with digitalis or diuretics, diabetes mellitus; [at admission] mechanical heart failure or electrical heart failure [ventricular fibrillation, ventricular tachycardia, auriculoventricular block, atrial fibrillation]), the 2-sided p value is 0.0052. When the difference is adjusted for secondary risk factors, the 2-sided p value is between 0.017 and 0.025, depending on the model. In the placebo group, 109 patients were withdrawn from study treatment and the corresponding number was 102 in the acebutolol group (Figure 4). The reasons for withdrawal are listed in Table V. Side-effects of β blockade were infrequent causes of withdrawal. The investigators rated the compliance over 90% of the theoretical number of tablets in 86.4% of the occasions in the acebutolol group and 85.4% in the placebo group and below 50% in 5.1 and 4.3% of the occasions, respectively.

The frequencies of clinical events as reported on study forms are listed in Table VI. Signs of heart failure were more frequent in the acebutolol group ($p = 0.003$), whereas death due to heart failure was not more frequent (3 against 7 deaths in the placebo group, Table IV) nor was acute pulmonary edema (Table VI). Bradycardia was more frequent in the acebutolol group ($p < 0.001$), whereas in turn, tachycardia was less frequent ($p = 0.002$, Table VI). Regarding nonvascular events or signs, diarrhea occurred more frequently in the acebutolol group ($p = 0.014$). Concomitant treatments were evenly distributed in the 2 groups. Thirty percent of the patients have taken aspirin regularly; one-half were given oral anticoagulants. One-third were given diuretics, whereas 10% received digitalis. Finally, 39.3% in the acebutolol group and 37.9% in the placebo group received nifedipine.

DISCUSSION

This trial has failed to select high-risk patients recovering from an AMI. The observed total mortality in the control group was 11% over 320 days. Assuming the hazard rate is constant, and extrapolated 1-year mortal-

ity is 12.5%, which is well below the expectation (>20%), although it is greater than the average 1-year mortality in the placebo groups of the previous trials and not different from the risk observed in the Norwegian propranolol trial,⁷ the Norwegian Multicenter Study⁹ and the Australian and Swedish Pindolol Study.³ Because a comparison of a β blocker against placebo in postAMI patients was felt ethical only if the basal 1-year mortality was in the unexplored range (i.e., >15 to 20%), the APSI Policy Board decided to terminate the trial early. Reasons that explain this failure will be considered in a separate report. Briefly, the selection algorithm works fairly well on average. However, the highest risk patients were not included, as shown by comparing the risk profiles of randomized and excluded patients in the 7 centers that kept the registry. Although recruitment in the trial had been stopped before its

scheduled termination because the included patients differed from the target population, our findings show a benefit from acebutolol as compared to placebo in terms of both total mortality, the primary outcome and vascular mortality. A metaanalysis conducted on the 12 trials confirms that in APSI, the decrease in 1-year mortality is at least as good as the pooled benefit (Figure 5). Actually, the observed decrease of 48% is the greatest observed among the 12 trials. However, this is not proof that acebutolol is more effective than any other β -blocking agent in the secondary prevention after myocardial infarction, although the p value for homogeneity is small when APSI is added to the other trials (0.023); the 95% confidence interval for the decrease is 0.27 to 0.90. It has been claimed that β -blocking agents with intrinsic sympathomimetic activity are less effective if not ineffective in that condition because the 2 trials that

FIGURE 5. Beta-blocking agents and post-myocardial infarction 1-year mortality. APSI = Acebutolol et Prévention Secondaire de l'Infarctus; ASPS = Australian and Swedish Pindolol Study; BHAT = Beta Blocker Heart Attack Trial; EIS = European Infarction Study; LIT = Lopressor Intervention Trial; MIS = Multicentre International Study; NMS = Norwegian Multicentre Study.

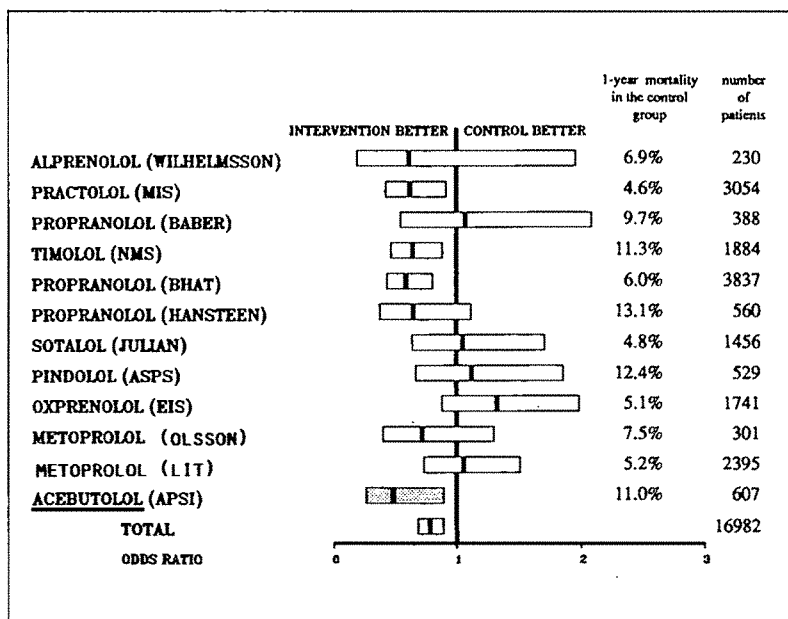
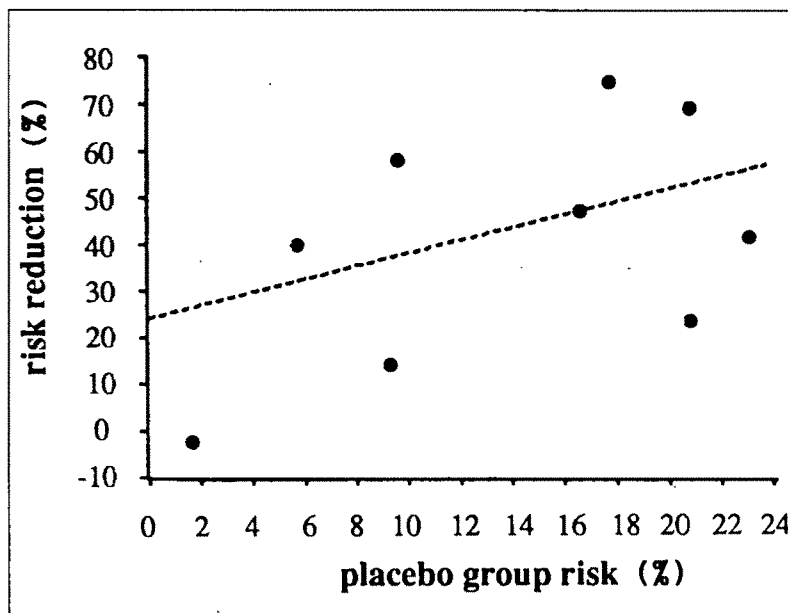


FIGURE 6. Regression of risk decrease over placebo subgroup risk (weighted by events).



tested such drugs, the European Infarction Study with oxprenolol and the Australian European Pindolol Study, gave negative trends.^{6,3} However, no overview of previously published trials has substantiated such a claim which, eventually, is even less likely after our findings because acebutolol is a β -blocking drug with intrinsic

sympathomimetic activity, however moderate. Nevertheless, a possible role of the daily dose of drugs cannot be discarded because we have chosen a rather low acebutolol dose. From a trial by Collett et al,¹⁹ acebutolol appears to be 4 to 7 times less potent on a mass basis than propranolol on exercise tachycardia in healthy vol-

TABLE VIII Comparison of APS and β BPP Subgroup Findings

	No. patients	BBPP		No. Patient	APSI	
		Death Rate (placebo)	Common Odds Ratio		Death Rate (placebo)	Common Odds Ratio
		1 yr			45.7 weeks	
Total no. patients	13,679	7.2	0.76	607	11.0	0.49
Age (yrs)						
<50	3,106	3.5	0.97	92	8.3	0.52
50 to 59	5,348	6.9	0.63	133	3.2	1.37
>59	5,225	9.8	0.83	381	14.1	0.43
Gender						
Male	11,398	7.1	0.74	442	9.4	0.51
Female	2,281	7.7	0.81	164	15.3	0.46
Interval AMI/randomization (days)						
<6	1,126	1.5	0.65	128	16.9	0.18
6 to 13	7,908	7.2	0.74	318	9.0	0.96
14 to 21	3,104	6.7	0.70	154	10.0	0.22
21	1,526	5.4	1.12	5	0	
Prior AMI						
Present	2,117	13.9	0.68	141	16.7	0.57
Absent	11,562	6.0	0.79	464	9.3	0.45
Prior angina pectoris						
Present	4,508	10.2	0.74	251	14.8	0.35
Absent	9,171	5.8	0.75	354	8.3	0.67
Prior heart failure						
Present	797	13.9	0.87	165	11.7	0.55
Absent	9,268	7.1	0.78	441	10.8	0.46
Prior SH						
Present	2,973	9.3	0.75	198	11.8	0.41
Absent	7,552	7.5	0.80	404	10.7	0.54
Prior diabetes mellitus						
Present	920	8.2	0.88	93	11.4	0.16
Absent	12,199	6.9	0.75	513	10.9	0.56
Treatment with digitalis						
Present	957	18.8	0.63	16	0	0.91
Absent	9,280	6.8	0.81	590	11.2	0.47
Treatment with diuretics						
Present	1,438	11.9	0.77	121	17.2	0.68
Absent	8,799	7.2	0.78	485	9.4	0.42
Electrical failure						
Present	4,487	8.3	0.68	219	11.0	0.49
Absent	8,663	6.3	0.77	388	11.0	0.49
Mechanical failure						
Present	3,519	12.8	0.73	311	13.9	0.46
Absent	10,160	5.3	0.78	296	8.2	0.51
Heart rate (beats/min ⁻¹)						
<70	3,339	4.5	0.74	214	7.3	0.50
70 to 89	8,076	6.7	0.75	291	11.3	0.47
>89	1,478	13.6	0.68	88	20.9	0.27
Diastolic BP (mm Hg)						
<70	2,059	6.5	0.54	275	14.1	0.09
70 to 89	8,016	6.7	0.79	236	9.7	1.02
>89	2,242	7.1	0.72	83	5.4	0.80
Systolic BP (mm Hg)						
<110	2,625	7.0	0.51	166	14.3	0.31
110 to 139	7,599	6.5	0.81	290	10.9	0.42
>139	2,115	7.1	0.79	138	8.3	0.71

APSI = Acebutolol et Prévention Secondaire de l'Infarctus; BBPP = β Blocker Pooling Project; SH = systemic hypertension.
BBPP findings from Ref. 15.

unteers.¹⁹ Hence, the daily dose of acebutolol that corresponds to the 320 mg daily dose of propranolol in the Beta Blocker Heart Attack Trial¹⁵ is $\leq 1,380$ mg. Thus, in APSI, the dose of β -blocking activity was one third of that in Beta Blocker Heart Attack Trial.

Although the trial sample was less at risk than expected for proving that β -blocking agents are still beneficial in high-risk patients, could we find evidence from our data that support this hypothesis? First, as mentioned before, the risk decrease is not different for the 329 patients with 6 to 8 secondary risk factors than for the 278 with >8 secondary risk factors, whereas the 45.7 weeks mortality on the placebo subgroups were 7.6 and 15.1%, respectively. Second, by subgrouping the study sample by the number of secondary risk factors, with ≥ 25 patients in every subgroup, a range of 45.7 weeks mortality from 1.8 to 23.1% was obtained; as shown in Figure 6, a trend, although not statistically significant, for increasing risk decrease with increasing risk does appear. Third, using the same subgrouping as in the Beta-Blocking Pooling Project,¹⁵ again no correlation with death rate in the placebo subgroups appeared (Table VIII). In the subgroups with "high-risk" prognostic factors such as electrical or mechanical failures, the 45.7 week mortality rate in APSI was between 10.2 and 20.9%, but for patients with digitalis the number was too small. The risk decrease in mortality ranges from 91% (diastolic pressure <70 mm Hg) to only 3% (prior mechanical failure) whereas in the alternative subgroups with "low-risk" prognostic factors, the decrease is between 48% (age <50 years) and 20% (diastolic blood pressure >89 mm Hg). One can note from Table VIII that the 45.7-week death rate in the placebo subgroup in APSI is almost always higher than in the pooled placebo subgroups from the Beta-Blocking Pooling Project. This confirms that patients in our trial were at higher risk than the average patient in the previous trials included in the Beta-Blocking Pooling Project. Heart rate decrease has been claimed as the key mechanism of the favorable effect of β -blocking drugs in postAMI patients.²⁰ However, the heart rate decrease in APSI was 9.2 beats/min, which is about the same as in the European Infarction Study (8 beats/min)⁶ or the Multicentre International Study (9 beats/min)¹ with a 29.4% observed increase in total mortality and a 20.5% observed decrease in total mortality, respectively.

Although the objective of our trial in terms of basal risk of the study sample has not been achieved, its findings, added to the previously published data, support that moderately severe patients after AMI can benefit from a β -blocking treatment. Furthermore, this trial has shown that acebutolol, a β -blocking drug with intrinsic sympathomimetic activity can decrease mortality in patients recovering from an AMI by 48%. Finally, our data, compared to previously published data, raise the point of the appropriate dose of β -blocking activity for secondary prevention in postAMI patients. However, the benefit/risk ratio of such a treatment is not documented for patients with very high risk (e.g., 1-year mortality $>20\%$). In addition, profiles of patients who

should not receive a β -blocking drug after an AMI have not been identified.

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APPENDIX

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Improved Survival but not Left Ventricular Function with Early and Prehospital Treatment with Tissue Plasminogen Activator in Acute Myocardial Infarction

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One hundred ninety patients with acute myocardial infarction (AMI) were treated with recombinant tissue-type plasminogen activator (rt-PA) 2.0 ± 0.8 hours after the onset of symptoms. Eighty-seven patients were enrolled via mobile intensive care units and 103 through the emergency ward. Patients who were enrolled via the mobile intensive care units were randomized to immediate, prehospital treatment initiation, or to delayed, in-hospital treatment initiation. All 190 patients except 2 underwent delayed coronary angiography and, when indicated, angioplasty at 72 hours after enrollment. Patients treated within 2 hours and those treated 2 to 4 hours after symptom onset had similar preservation of left ventricular function, and similar prevalence of congestive heart failure at discharge. Patients treated within 2 hours of symptom onset had significantly lower short- (0.0 vs 6.3%, $p = 0.01$) and long-term (1.0 vs 9.5%, $p = 0.03$) mortality. Prehospital initiation of rt-PA appeared to be safe and feasible and resulted in a 40-minute decrease in the time from symptom onset to treatment initiation.

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Time to treatment is one of the most important determinants of successful thrombolysis in acute myocardial infarction (AMI). Thrombolytic treatment initiated within 2 hours after onset of pain has been shown to be most effective in preserving left ventricular function¹⁻³ and reducing short- and long-term mortality.⁴⁻⁶ The purpose of the first phase of the Israeli Study of Early Intervention in Myocardial Infarction was to identify possible correlates of clinical outcome in patients with AMI after thrombolytic treatment with recombinant tissue-type plasminogen activator (rt-PA) with special emphasis on time from onset of symptoms to thrombolytic treatment. We report the main results observed in 190 patients with AMI, in whom rt-PA thrombolysis was initiated an average of 2 hours after onset of symptoms. Prehospital thrombolysis was initiated in a substantial portion of these patients by the teams of the mobile intensive care units. Patients underwent coronary angiography 72 hours after treatment initiation, and, when indicated, coronary angioplasty or coronary bypass. Short- and long-term effects of early versus late thrombolytic therapy were evaluated by left ventricular function, cardiac morbidity and mortality.

METHODS

Study population: From October 1986 to December 1987, 190 consecutive patients received rt-PA therapy for AMI. Patients were enrolled via the emergency ward and the mobile intensive care units, which were staffed by a physician and paramedic. Patients who were brought in by the mobile intensive care units were randomized by a month into prehospital or in-hospital treatment groups. Months for each of the 2 treatment modes were selected randomly. In patients recruited during the months selected for prehospital treatment, rt-PA infusion was initiated at home, whereas in patients recruited during the months selected for in-hospital treatment initiation, rt-PA infusion was initiated only after admission to the intensive coronary care unit. When a patient with AMI was identified by the mobile unit team as eligible for thrombolytic therapy, the team would radio the senior physician on call and describe

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TABLE I Clinical Outcome of Patients with Anterior, Inferior and Old Infarction

	Inferior Infarction (n = 89)	Anterior Infarction (n = 76)	Previous Infarction (n = 25)	p Value
Left ventricular ejection fraction (%)				
Immediate*	57 ± 11	40 ± 15	42 ± 14	0.0001
Contrast†	61 ± 13	58 ± 13	52 ± 13	0.01
Discharge*	56 ± 13	46 ± 17	42 ± 16	0.0001
Clinical outcome at discharge (%)				
Congestive heart failure	1/87 (1)	7/74 (10)	5/25 (20)	0.003
Mortality at 60 days	2/89 (2)	3/76 (4)	1/25 (4)	NS
Mortality at 24 months	4/89 (4)	4/76 (5)	2/25 (8)	NS

* Determined by radionuclide ventriculography; † determined during coronary angiography at 72 hours.

TABLE II Clinical Outcome of Patients with 1-, 2- and 3-Vessel Coronary Artery Disease

	One-Vessel Disease (n = 90)	Two-Vessel Disease (n = 61)	Three-Vessel Disease (n = 37)	p Value
Ventricular function				
Immediate LVEF	48 ± 15	49 ± 15	50 ± 16	NS
Pts (n)	(80)	(57)	(34)	
Discharge LVEF	52 ± 15	51 ± 15	48 ± 17	NS
Pts (n)	(90)	(59)	(31)	
Change in LVEF	+4	+2	-2	NS
% patients with normal (>50%) discharge LVEF	60/90 (67)	38/56 (64)	17/37 (46)	0.08
Congestive heart failure at discharge (%)	6/90 (6)	3/61 (3)	6/37 (14)	0.059
Non-Q-wave infarction (%)	30/90 (33)	18/61 (30)	3/37 (8)	0.01
Mortality at 30 days†	1/90 (1)	2/61 (3)	4/37 (11)	0.029
Mortality at 24 months†	1/90 (1)	3/61 (5)	4/37 (11)	0.049

* By Wilcoxon rank sum test.

† Excluding the 2 patients who died before angiography could be done. Tested by Fisher exact test for 2 × 2 tables — 3 versus 1- + 2-vessel disease.

LVEF = left ventricular ejection fraction.

the patient's history and electrocardiographic picture. Based on this verbal description, the physician in charge authorized treatment initiation and allocated a bed in one of the intensive coronary care units involved in the study. During the randomized months in which treatment was delayed until after admission to the coronary care unit, the same procedure of communicating with and obtaining the approval of the senior physician was followed, but the mobile unit team did not start treatment and thrombolytic infusion was initiated in the hospital coronary care unit.

Patients enrolled through the emergency ward were treated as soon as possible after admission, with rt-PA infusion initiated either in the emergency room, or on admission to the intensive coronary care unit. The study protocol was approved by both institutional committees on human research, and all participating patients gave their informed consent.

ENTRY CRITERIA: All patients admitted to the study were <72 years old, had severe chest pain for >30 minutes, but not >4 hours, had ST-segment elevation of 0.1 mV in at least 2 contiguous electrocardiographic leads, had no left bundle branch block on the entry electrocardiogram, no history of congestive heart failure, no prior cardiac surgery, a diastolic blood pressure <120 mm Hg, no history of terminal illness and no bleeding

predisposition (i.e., oral anticoagulant therapy, recent trauma, past bleeding history, or cerebrovascular accident during the last 6 months).

THROMBOLYTIC REGIMEN: A total dose of 120 mg rt-PA (G11035, supplied by Boehringer Ingelheim) was administered during a 6-hour infusion starting with a 10 mg bolus followed by a continuous infusion of 50 mg during the first hour, 20 mg in the second hour and 10 mg during each of the following 4 hours.

Concomitantly, heparin was infused intravenously, starting with a bolus of 5,000 IU and continuing with 25,000 IU/24 hours. Dose was adjusted thereafter to maintain the activated partial thromboplastin time between 1.5 to 2 times each patient's baseline value. Heparin infusion was continued for at least 5 days except in the following cases: patients who underwent successful coronary angioplasty where heparin was discontinued after 24 hours; patients who had bleeding; and patients who were referred to urgent (before discharge) coronary bypass surgery, where heparin was continued until surgery. Aspirin in a daily dosage of 250 mg was started after the first 24 hours and was continued during follow-up. Conventional antianginal and anticongestive therapy was administered as needed. All patients were treated prophylactically with 2 g/day of intravenous lidocaine for the first 24 hours.

TABLE III Baseline Characteristics of the Study Patients

	Enrollment by Mobile Coronary Unit			Enrollment by Time to Treatment	
	Prehospital (n = 43)	In-Hospital (n = 44)	Emergency Ward (n = 103)	<120 min (n = 96)	≥120 min (n = 94)
Age (yrs)	59 ± 7	58 ± 8	56 ± 10.0	57 ± 8	57 ± 10
Sex (% male)	79.1	81.8	88.3	81.0	88.0
Clinical prognostic groups					
Anterior AMI (%)	37.2	31.8	44.6	54.1	39.4*
Inferior AMI (%)	46.5	47.7	46.7	32.4	47.8
Previous AMI (%)	15.3	20.5	8.7	13.5	12.8
Angina pectoris (% patients)					
Absent	46.5	52.3	54.3	49.0	55.0
<6 months	27.9	36.4	34.9	32.3	35.1
>6 months	25.6	11.4	10.6	18.7	9.5
Functional classification† (% patients)					
0 to 1	81.0	84.1	87.3	81.3	89.3
2 to 3	19.0	15.9	12.6	18.7	10.8
Rales over 1/3 lung fields (% patients)	19.0	9.3	10.6	15.6	8.5‡
% pts with 2- and 3-vessel CAD	48.8	60.5	56.4	53.1	57.7
Time to treatment (min)	1.6 ± 0.6	2.2 ± 0.7	2.0 ± 0.8	1.3 ± 0.4	2.7 ± 0.5

* Statistical difference between the prevalence of anterior wall infarction in the early (<120 min) versus late (≥120 min) treatment groups, p = 0.06.
† By Canadian classification.
‡ Time to treatment <120 versus ≥120 min, p = 0.05.
§ p < 0.0001.
All ± data are mean ± standard deviation.
AMI = acute myocardial infarction; CAD = coronary artery disease.

TABLE IV Clinical Outcome of the Study Patients

Treatment Group	Enrollment by Mobile Coronary Unit			Enrollment by Time to Treatment	
	Prehospital (n = 43)	In-Hospital (n = 44)	Emergency Ward (n = 103)	<120 min (n = 96)	≥120 min (n = 94)
Left ventricular function (% LVEF)					
Immediate LVEF	48 ± 15	48 ± 15	49 ± 15	48 ± 15	49 ± 16
Pts (n)	(37)	(41)	(87)	(79)	(86)
Discharge LVEF	50 ± 14	45 ± 18	54 ± 16	51 ± 14	49 ± 18
Pts (n)	(43)	(44)	(99)	(95)	(93)
Percent patients with patent infarct artery	82	77	87	83	85
Congestive failure at discharge (% pts)	2	14	6	7	7
Non-Q-wave MI (% pts)	28	23	28	32	22

* p = 0.07.

CORONARY ANGIOGRAPHY AND PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY: All patients underwent coronary angiography 72 hours after treatment initiation unless their clinical situation necessitated earlier catheterization. Patients with >50% reduction in the luminal diameter of the infarct-related artery underwent an ad hoc percutaneous transluminal coronary angioplasty during the same session unless they were referred to coronary bypass surgery because of 3-vessel coronary artery disease, left main or left main equivalent disease was found, the infarct artery was considered insignificant or the lesion was not considered suitable for angioplasty for other reasons. The decision to proceed to angioplasty was based on coronary anatomy revealed during angiography. The treating physicians

were unaware of the time interval from onset of symptoms to the initiation of thrombolytic infusion. Similarly, the decision to refer patients to bypass surgery was based on the angiographic characteristics of each patient, and this decision was made by an institutional committee whose members were blinded to the time to treatment after the onset of infarction.

Patency of the coronary arteries was evaluated by a central angiography committee. The assessment involved a consensus reading of all angiograms by the same 2 coronary angiographers, who were blinded to the clinical course of the patients except for the electrocardiographic localization of the infarction. Severity of coronary artery disease was determined by visual assessment of the reduction in luminal diameter (percent ste-

TABLE V Mortality by Enrollment Groups and Time to Treatment

Time to Treatment	Enrollment by			Total	p Value*
	Mobile Coronary Unit Prehospital	In-Hospital	Emergency Ward		
<120 minutes	n = 33	n = 14	n = 51	n = 96	
≥120 minutes	n = 10	n = 10	n = 52	n = 94	
All patients	n = 43	n = 44	n = 103	n = 190	
Mortality at 60 days					
<120 minutes	0	0	0	0	
≥120 minutes	1	3	2	6	0.01
Mortality at 24 months (all)					
<120 minutes	0	0	1	1	
≥120 minutes	3	3	3	9	<0.01
Mortality at 24 months (cardiac only)					
<120 minutes	0	0	1	1	
≥120 minutes	1	3	3	7	0.03

* Statistically significant: difference in mortality between the total early and late treatment groups. Examined by Fisher's exact test for 2 × 2 tables.

nosis) and Thrombolysis in Myocardial Infarction (TIMI) gradings of perfusion of each coronary artery and its major branches.⁷

EVALUATION OF LEFT VENTRICULAR FUNCTION: During hospitalization, each patient underwent 3 radionuclide studies to assess left ventricular function. These studies were performed as soon as possible after admission, but not later than 48 hours (mean 18 ± 13 hours), immediately before the 72-hour coronary catheterization, and at discharge. Only the results of the first and last studies are reported here. For analysis purposes, the 5 patients who died before discharge were assigned a discharge left ventricular ejection fraction of zero. A separate analysis of left ventricular ejection fraction was performed, eliminating the 5 patients who died, but results remained similar.

Radionuclide studies were performed in the nuclear cardiology laboratories adjacent to the coronary care unit. An Elscint Apex 415 digital gamma camera was used and a multigated equilibrium blood pool scan with red blood cells labeled in vivo with 20 to 25 mCi of technetium-99m was performed in the anterior and 45° left anterior oblique projection. Left ventricular ejection fraction was determined in the 45° left anterior oblique projection. A background-corrected left ventricular time activity curve was used to calculate the global ejection fraction semiautomatically. All radionuclide examinations and the left ventricular ejection fraction were assessed by the same 2 experienced cardiologists who were blinded to the clinical course of the examined patients.

Clinical definitions: **INFARCTION:** The diagnosis of myocardial infarction was confirmed by the occurrence of ischemic chest pain lasting >30 minutes and accompanied by ST-segment elevation of at least 0.1 mV in 2 contiguous electrocardiographic leads, followed by either an increase of creatine kinase-MB fraction to values >5% of total creatine kinase, or appearance of a Q wave not present on entry electrocardiogram.

PATENCY: A TIMI grade of 2 or 3 for the infarct-related coronary artery was defined as patent.⁷ Occluded infarct-artery was accordingly defined as TIMI grade 0 or 1.

CLINICAL PROGNOSTIC GROUPS: For the purpose of analysis, patients were categorized into 3 groups: one with first infarctions in the anterior wall and no prior infarction, one with an infarction in the inferior wall and no prior infarction, and one with a previous myocardial infarction irrespective of the location of the current infarction.

Statistical analysis: The 2 randomized groups that were enrolled via the mobile intensive care units were compared to the group enrolled through the emergency ward. This analysis indicated that treatment earlier than 120 minutes after symptom onset had a beneficial effect on mortality irrespective of enrollment group. This 120-minute cut-off point is consistent with earlier reports.^{1,4,6} Consequently, all baseline and outcome variables were compared in patients treated within 120 minutes and patients treated ≥120 minutes after onset of symptoms.

Continuous variables that differed between groups were analyzed by *t* test (when 2 groups were compared) or 1-way analysis of variance (when 3 groups were compared), or Wilcoxon's rank sum test when variances were unequal. For categorical variables, chi-square or Fisher's exact test for 2 × 2 tables were used.

RESULTS

Study population: One hundred ninety patients with AMI received intravenous rt-PA infusion. There were 161 men and 29 women who were 56 ± 9.4 and 62 ± 7.1 years old, respectively ($p < 0.001$). Except for age, there was no significant difference between men and women in either baseline characteristics or clinical outcome; therefore, they were grouped together in all analyses. There were 165 patients (87%) with first myocardial infarction, of whom 76 (40%) had anterior wall and 89 (47%) inferior wall infarctions. An additional 25 patients (13%) had a previous AMI.

Of the 190 patients, there were 8 in whom the initial clinical picture of AMI was not confirmed by an increase of the MB fraction of creatine kinase or by the development of new Q waves during hospitalization. However, analysis was performed on the total group,

because excluding these patients did not affect the results.

Clinical prognostic groups: Patients with first anterior and inferior wall AMI and patients with a previous AMI had similar baseline characteristics except that the latter had more diffuse coronary artery disease ($p < 0.01$) as demonstrated by a significantly higher prevalence of 2- and 3-vessel disease (92% vs 41 to 51%). The groups with first anterior wall AMI and with a previous AMI resembled each other and had a significantly larger infarct size and less preservation of left ventricular function immediately after admission, during coronary angiography, and at discharge compared to patients with first inferior wall AMI (Table I). Patients with anterior wall AMI and patients with previous AMI also had a higher mortality rate at 60 days, but this excess was not statistically significant. At 24 months, higher mortality was observed in patients with first anterior compared to patients with first inferior AMI; however, this difference was not significant. Within the group of patients with a previous AMI, the infarct site had no effect on outcome (data not shown).

Coronary angiography and angioplasty: Coronary angiography was performed within 72 hours after commencement of rt-PA infusion in 188 patients; 2 patients died before coronary angiography could be done. The infarct artery was found to be patent in 158 patients (84%) with a normal coronary angiogram found in 4 of them. Ninety patients (47%) had 1-vessel, 61 (32%) had 2-vessel, and 37 (19%) had 3-vessel coronary artery disease.

The outcome in patients with the most diffuse 3-vessel coronary artery disease was significantly worse compared to that in patients with 1- and 2-vessel disease; outcome was similar in the latter 2 groups (Table II). The worse outcome was manifested by lower incidence of non-Q-wave infarction, lower percentage of normal ($>50\%$ ejection fraction) left ventricular function at discharge and increased mortality at 60 days and 1 year.

Time to treatment: Table III lists demographic and clinical characteristics of patients by enrollment group at entry. Of the 190 patients, 103 were admitted via the emergency ward and were treated within 2.0 ± 0.8 hours from onset of symptoms. Eighty-seven patients were brought in by the mobile units; 43 were randomly assigned to prehospital treatment initiated at home, and 44 to delayed treatment in the hospital's coronary care unit, with 1.6 ± 0.6 and 2.2 ± 0.7 hours to treatment, respectively ($p < 0.001$). Mean time to treatment in patients who were enrolled via the mobile coronary units was 1.9 ± 0.8 hours, and thus was similar to the time to treatment in the patients who enrolled via the emergency ward. The overall mean time from onset of symptoms to treatment initiation was 2.0 ± 0.8 hours.

The 43 patients whose treatment was initiated at home by the mobile intensive care unit teams did not experience any complications during transfer, including bleeding, allergic reactions or hypotension. Two patients had ventricular fibrillation, which was successfully converted by electrical defibrillation.

Of the total study group, 96 patients (50%) were

treated within 2 hours from onset of pain (early treatment group), and in 94 (49%) treatment was initiated between 2 and 4 hours after onset of pain (late treatment group). These 2 groups were comparable with respect to age and sex, but the group treated within 2 hours from symptom onset tended to be more severely ill, as reflected by a higher prevalence of anterior wall infarctions ($p = 0.06$), a longer history of anginal syndrome, and a worse Killip class.

Mechanical revascularization procedure: Coronary angioplasty was performed in 96 patients (50%) and was successful (defined by $>50\%$ reduction in luminal stenosis) in 85 patients (88%). As expected from their worse baseline clinical characteristics, coronary angioplasty and coronary bypass operations were performed more often in the patients in the early treatment groups than in the late treatment groups. Thus, 56 versus 45% underwent coronary angioplasty in the early and late treatment groups, respectively (difference not significant), and 14 versus 4% of the patients in the 2 groups underwent coronary bypass operations before discharge ($p = 0.02$). This higher incidence of mechanical revascularization procedures in the early treatment group was highly significant ($p < 0.01$).

Clinical outcome of early versus late treatment groups: All outcome variables except mortality were unaffected by the time or place in which treatment was initiated (Table IV). Patients in all enrollment categories had similar preservation of left ventricular function, similar incidence of congestive heart failure at discharge and similar patency rates at the 72-hour angiography.

Mortality was significantly lower in the early treatment group (Table V). None of the 96 patients in the early treatment group died within 60 days after the infarction, whereas 6 patients among the 94 patients in the late treatment group died ($p = 0.01$). Of these 6 deaths, 1 occurred 10 minutes after treatment initiation and was related to persistent ventricular fibrillation; the other 5 patients died from cardiogenic shock. Four additional deaths occurred >2 months after treatment, 1 from the early treatment group and 3 from the late treatment group. The patient in the early treatment group died of cardiogenic shock 3 months after treatment. In the late treatment group, 1 patient died of ruptured mycotic-aortic-aneurysm after 3 months, another died of anaphylactic shock after 3 months and the third died in an accident 24 months after treatment. Thus, mortality at 24 months was significantly lower for the early treatment group (1 of 96, 1%) than for the late treatment group (9 of 94, 10%) ($p < 0.01$) (Table V). The difference was still significant when only the 8 cardiac deaths were considered ($p = 0.03$).

DISCUSSION

The importance of early thrombolytic therapy has been demonstrated in 2 large scale mortality studies; the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto miocardico and the Anisoylated Plasminogen Streptokinase Activator Complex Intervention Mortality Studies.⁴⁻⁶ In our study population, the overall 2-year mortality rate was low: 10 deaths out of 190 treated

patients (5%), of which 8 (4%) were cardiac. This low mortality may be related, at least in part, to the fact that thrombolytic therapy was initiated an average of 2 hours after symptom onset. Moreover, our patients treated within 2 hours from symptom onset had significantly lower 60-day and 24-month mortality when compared to the patients treated 2 to 4 hours after symptom onset.

It is noteworthy that the 96 patients who received early thrombolytic therapy were more severely ill, as indicated by the increased incidence of preinfarction angina pectoris, the worse Killip class at admission and the significantly higher incidence of mechanical revascularization procedures. This suggests that sicker patients seek help earlier. Thus, patients who were treated earlier had lower mortality, even though they comprised a higher risk population.

It is also noteworthy that only 4 deaths (2%) occurred in all of these patients between 60 days and 24 months. However, this remarkably low long-term mortality should be viewed with respect to the overall low mortality in our population of AMI patients treated with thrombolytic therapy, and the previous experience gathered in other thrombolytic trials, which demonstrated that most of the deaths in these patients occurs in the first 2 months.⁵

Although it can be argued that the lower mortality in the early treatment group is related to the higher incidence of mechanical revascularization procedures, it should be stressed that all patients underwent coronary angiography within 72 hours after enrollment, that the decision to proceed with coronary angioplasty or bypass operation was based on objective anatomical criteria and that the decision-making process was conducted by physicians who were blinded to the time elapsed from onset of symptoms to treatment initiation.

While others have also found that early treatment is associated with reduced mortality, the relation between early treatment and improvement of left ventricular function is less clear. Some studies observed better preservation of left ventricular function in patients treated earlier,¹⁻³ whereas others have found no relation between preservation of left ventricular function and time to treatment.⁸⁻¹⁰ In our study, despite the lower mortality of patients treated earlier, other clinical parameters such as left ventricular ejection fraction, prevalence of congestive heart failure at discharge or the incidence of non-Q-wave infarction did not differ between early and late treatment groups. Similar discrepancy between the effects of reperfusion on left ventricular function and survival was recently reported in patients treated with anisoylated plasminogen streptokinase activator complex versus patients treated with heparin.¹¹ It has been argued that assessment of global left ventricular function may be misleading in the early stage of acute infarction because of myocardial "stunning."¹²

Most of the advantage of thrombolytic therapy is achieved when it is administered early during the course of myocardial infarction. Unfortunately, most patients with AMI wait 1 to 2 hours before they seek medical help, and thus they reach treatment with an AMI that is already 2 to 3 hours old. By the time medical care is received, the amount of salvageable myocardium is deteriorating rapidly and each minute counts. The overall better outcome of patients in our early treatment group may be in part attributed to the initiation of rt-PA infusion in the homes of some patients by the mobile intensive care units. On the basis of our experience, such early intervention is safe and effective, and we recommend it whenever appropriate facilities are available. The additional cost of providing thrombolytic therapy through existing mobile coronary care units is negligible. Thus, prehospital thrombolytic therapy can augment the success of such treatment by shortening the interval between symptom onset and treatment initiation, and may thereby reduce mortality.

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Effects of Early Intervention with Low-Dose Aspirin (100 mg) on Infarct Size, Reinfarction and Mortality in Anterior Wall Acute Myocardial Infarction

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Recently, it was shown that aspirin given early in acute myocardial infarction (AMI) improves hospital survival, but the mechanisms involved are unclear. In a prospective, randomized placebo-controlled trial, the influence of early intervention with low-dose aspirin (100 mg/day) on infarct size and clinical outcome was studied in 100 consecutive patients with first anterior wall AMI. Infarct size was calculated by cumulative lactate dehydrogenase release in the first 72 hours after admission and was found to be (mean \pm standard deviation) $1,431 \pm 782$ U/liter in the aspirin group ($n = 50$) and $1,592 \pm 1,082$ U/liter in the placebo group ($n = 50$, $p = 0.35$). The study medication was given for 3 months, during which mortality was 10 (20%) in the aspirin patients and 12 (24%) in the placebo patients ($p = 0.65$). However, reinfarction occurred in 2 patients (4%) in the aspirin group and in 9 (18%) in the placebo group ($p < 0.03$).

Early intervention with low-dose aspirin showed, in comparison to placebo, a 10% decrease of infarct size, but this difference was not statistically significant. However, early low-dose aspirin effectively decreased the risk of reinfarction. Therefore, the favorable results of early aspirin on mortality in acute myocardial infarction are probably due more to prevention of reinfarction than to decrease of infarct size.

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The role of aspirin after myocardial infarction remains to be established. The major shortcoming in the postinfarction trials with aspirin is that most of them included patients who had an acute myocardial infarction (AMI) up to 6 years before the trial. Aspirin therapy was started earlier after AMI in only 2 trials. The first trial randomized patients within 1 week after AMI and showed a trend toward better survival with aspirin 900 mg/day.¹ These findings were confirmed by the results of the International Study of Infarct Survival trial-2, which showed that low-dose aspirin (160 mg/day) within 24 hours after symptom onset improves survival of patients with AMI, whether or not the patients received thrombolytic therapy.² The mechanisms by which early low-dose aspirin improves survival in AMI have not been elucidated. Specifically, it is unknown whether aspirin decreases infarct size, improves left ventricular function or decreases thrombotic events. Experimental studies indicate that aspirin increases collateral blood flow after coronary occlusion.^{3,4}

The purpose of this prospective, randomized placebo-controlled trial was to determine whether early intervention with low-dose aspirin (100 mg/day) in patients with first anterior wall AMI decreased infarct size or improved clinical outcome.

METHODS

Patients were eligible for entry if they had early (<12 hours) symptoms and electrocardiographic signs of first anterior wall AMI (ST-segment elevation of >2 mm in the precordial leads in the absence of precordial Q waves) and no contraindications to aspirin (recent gastrointestinal ulceration). Within 12 hours after hospital admission, informed consent was obtained and patients were then randomized to receive 1 capsule/day containing 100 mg acetylsalicylic acid or placebo. The first capsule was given immediately after informed consent and the study medication was continued for 3 months. Patient compliance was assessed by capsule counts. Further antithrombotic treatment consisted of heparin 5,000 U subcutaneously twice a day until complete mobilization. Standard coronary care was given to all patients.⁵ Thrombolytic therapy was given only to patients <70 years of age who had symptoms for <4 hours and no contraindications. Coronary artery bypass surgery or coronary angioplasty were performed for clinical indications only. Oral anticoagulants and open-label aspirin were not allowed during the study period, unless indicated.

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TABLE I Relevant Easeline Characteristics of Both Patient Groups

	Aspirin (n = 50)	Placebo (n = 50)
Age (mean \pm SD, yr)	61 \pm 13	64 \pm 13
Range (yr)	27 to 89	36 to 91
Men (%)	72	76
Previous infarction (%)	14	16
Previous angina (%)	24	28
Interval 1st symptom-Rx (mean \pm SD, min)	244 \pm 42	248 \pm 48

Rx = study medication; SD = standard deviation.

Infarct size was the primary endpoint of the trial. It was measured by cumulative serum-lactate dehydrogenase release in the first 72 hours after admission and was calculated according to methods described earlier.⁶ In brief, 5 ml samples of venous blood were obtained at admission every 12 hours for the first 2 days and daily for the following 3 days. The blood sample was allowed to clot and the activities of lactate dehydrogenase in the serum were measured. Hemolytic samples were discarded and new samples were ordered.

Clinical outcomes (death, reinfarction, unstable angina and revascularization) were secondary endpoints of this trial. Special attention was given to the recurrence of ischemic events. Unstable angina pectoris was defined as the occurrence of anginal pain at rest or with minimal physical activity with accompanying ST-segment changes on electrocardiography and normal plasma levels of creatine kinase MB 6 hours later. Reinfarction was diagnosed when anginal pain recurred together with ST-segment changes or new Q waves or both, followed by significant increase in creatine kinase MB, creatine kinase, serum glutamine oxalate transferase and lactate dehydrogenase to levels exceeding twice the upper limit of normal levels.

Analysis of the study endpoints was done according to the intention-to-treat principle. Statistical methods are given where applicable.

RESULTS

As planned, 100 patients entered the trial. Fifty patients received 100 mg aspirin daily and 50 received placebo. Their baseline characteristics are listed in Table I. There were no significant differences in relevant baseline data between the 2 patient groups.

Three months of follow-up data are complete in all patients. Twenty-one patients (21%) died in-hospital and 1 patient died during the follow-up. Eleven patients (11%) sustained recurrent myocardial infarction, all during hospital stay. The reinfarctions occurred between days 3 and 27 after the index infarction. Unstable angina pectoris was diagnosed during hospital stay in 25 patients (25%). The episodes of unstable angina were reported between day 3 and day 18 after the index infarction. Revascularization procedures were performed infrequently and none were done within the first week after admission. The study medication was withdrawn in patients who sustained reinfarction. In patients developing postinfarction unstable angina, the study medica-

TABLE II Clinical Outcome in Both Patient Groups During 3 Months Follow-Up

	Aspirin (n = 50)	Placebo (n = 50)
Mortality	10	12
Reinfarction	2	9
Unstable angina	14	11
CABG/PTCA	2	1

* $p < 0.03$, chi-square.
CABG/PTCA = coronary artery bypass graft/percutaneous transluminal coronary angioplasty.

tion was discontinued and replaced by open-label aspirin (100 mg/day). The study medication was not withdrawn, except for death, in any patient during the first 3 days after admission.

The clinical outcome of both patient groups is listed in Table II. Only the reinfarction rate was significantly decreased in patients receiving aspirin. None of the deceased reached other proven endpoints like unstable angina, reinfarction or revascularization. The 3 patients undergoing angioplasty or surgery had untractable post-infarction unstable angina pectoris, but no documented reinfarction. The 72-hour cumulative lactate dehydrogenase release (mean \pm standard deviation) for the index infarction was $1,431 \pm 782$ U/liter in the aspirin group versus $1,592 \pm 1,082$ U/liter in the placebo group (Figure 1, $p = 0.35$). Thus, early intervention

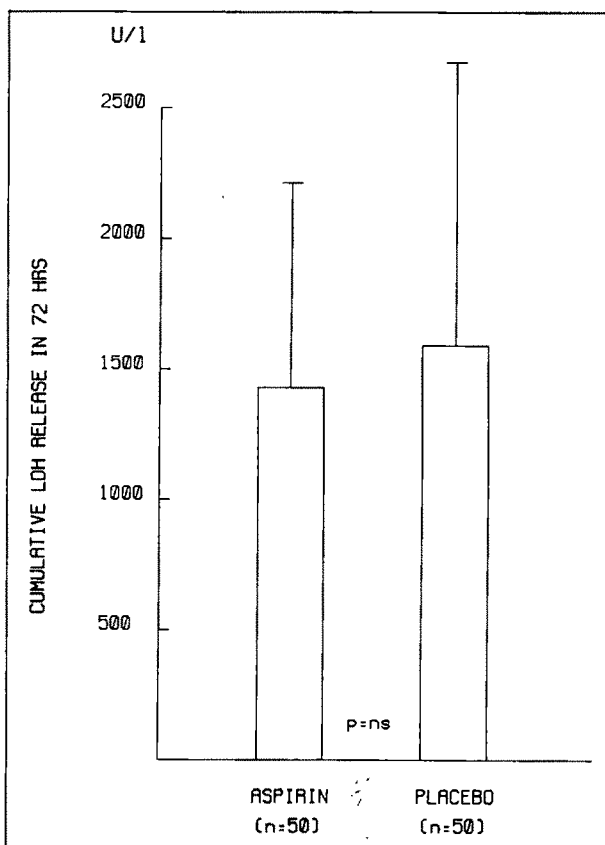


FIGURE 1. Enzymatic infarct size (mean \pm standard deviation) measured as cumulative lactate dehydrogenase (LDH) release during 72 hours after admission in patients treated with early low-dose aspirin and placebo.

with low-dose aspirin decreased the size of the index infarction by about 10%, but the difference with placebo was not statistically significant. Eleven patients (6 on aspirin and 5 on placebo) had incomplete enzyme sampling because of early (<72 hours) death and were not analyzed in the infarct size calculations.

Fifty patients (24 on aspirin and 26 on placebo) received thrombolytic therapy. Hospital mortality in this subset of patients was relatively low (4 patients [8%] of whom 2 received aspirin and 2 placebo). One reinfarction occurred in the aspirin group versus 6 in the placebo group ($p = 0.06$, chi-square). In the patients receiving thrombolytic therapy, the 72-hour cumulative lactate dehydrogenase release was $1,390 \pm 701$ U/liter in the aspirin group versus $1,600 \pm 699$ U/liter in the control group (Figure 2, difference not significant). In the patient group not receiving thrombolytic therapy, these values were $1,470 \pm 722$ U/liter in the aspirin group and $1,580 \pm 803$ U/liter in the placebo group (Figure 2, difference not significant). Thus, thrombolytic therapy, which was not randomized, did not appear to change the results of aspirin on infarct size.

Beta blockers were given to 15 aspirin patients and 17 placebo patients, calcium antagonists were given to 4 and 2 patients, respectively, and 2 patients in both groups received the combination. Oral anticoagulants were not given to any patient in the trial, nor was open-label aspirin for indications other than unstable angina. Thus, in the placebo group, 11 patients (22%) received aspirin after an episode of unstable angina pectoris.

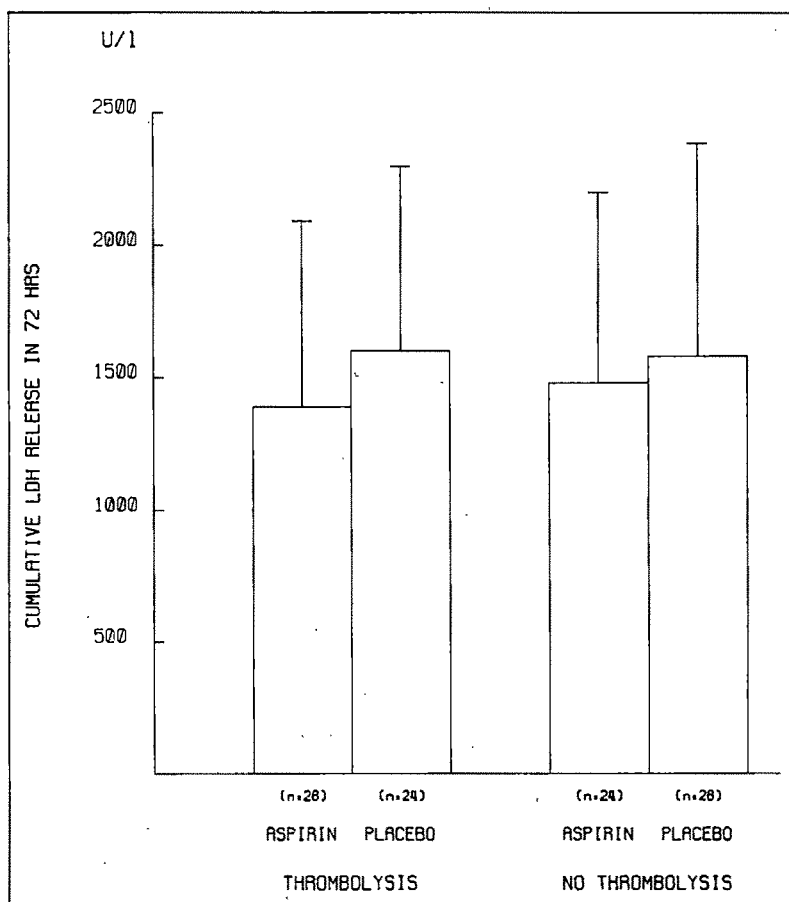
DISCUSSION

In this study we showed that early intervention with low-dose aspirin does not seem to influence infarct size significantly. However, we cannot rule out that aspirin decreases infarct size by a mere 10%. If the trend observed in this trial really reflects a small effect, a sample size of ≥ 500 patients (250 with aspirin and 250 with placebo) would have been necessary to achieve a significance level of $p < 0.05$. It is doubtful whether such a small effect would have any effect on infarct survival.

To the best of our knowledge, this is the first prospective study in humans on the influence of aspirin on infarct size. Experimental investigations indicated that in a model of AMI, high-dose aspirin (20 to 100 mg/kg) increases collateral blood flow.^{3,4} However, in these animals, aspirin was given 1 to 12 hours before coronary occlusion and, in our patients, about 4 hours after onset of symptoms. On the other hand, many individuals develop AMI while on aspirin for various reasons and the influence of aspirin pretreatment on the eventual infarct size is unknown. In The Physicians Health Study,⁷ which investigated the role of aspirin 160 mg/day in the primary prevention of myocardial infarction, infarct mortality was 5% in the aspirin group and 10% in the placebo group, suggesting some influence of aspirin pretreatment on the natural course of AMI.

Even in our small series of patients, early low-dose aspirin decreased the reinfarction rate significantly, especially in the patients undergoing thrombolytic therapy. The latter finding is not new. We were the first to

FIGURE 2. Enzymatic infarct size (mean \pm standard deviation) measured as cumulative lactate dehydrogenase (LDH) release during 72 hours after admission in patients treated with and without thrombolytic therapy and subsequently with early low-dose aspirin and placebo.



report this⁸ and we showed that the decrease of reinfarction rate was achieved by prevention of coronary reocclusion. The much larger International Study of Infarct Survival trial-2 confirmed the favorable results of aspirin with respect to reinfarction.² Apparently, hospital mortality of AMI is not only due to the size of the initial infarction, but also to the occurrence of reinfarction. Previous studies showed that early intervention with β blockers decreases reinfarction⁹ and hospital mortality.¹⁰ Therefore, strategies to prevent early reinfarction might well improve survival of AMI.

Early infarct extension does not seem to be significantly influenced by aspirin. For estimation of infarct size, we used the cumulative release of a slowly cleared enzyme like lactate dehydrogenase by the necrotic myocardium. If there would have been any effect of aspirin on early infarct extension, this would have appeared in the results. The method used in this trial for the calculation of infarct size has been validated in animals,¹¹ correlates well with left ventricular function,^{6,12} myocardial perfusion defects⁶ and survival^{6,13,14} and is insensitive to early coronary reperfusion by thrombolysis.¹⁴ Neither infarct size nor left ventricular function was assessed in the large previous aspirin trials in AMI.^{1,2} In our above mentioned reocclusion trial, we found a better left ventricular function after intravenous streptokinase with aspirin than without, but this was highly correlated with the occurrence of reinfarction.⁸

Patients treated with intravenous streptokinase in this trial had a low mortality, but did not show smaller infarcts than patients not eligible for thrombolysis, who have, by definition, a high hospital mortality.¹⁵ One should realize that we randomized for aspirin, not for thrombolysis. Furthermore, patients receiving thrombolysis in this trial were young (<70 years) and came in early (<4 hours of symptoms). As expected, they had a larger risk of reinfarction and this explains why aspirin provided an extra benefit in terms of reinfarction.

In this study we included only patients with first anterior AMI, because these patients have the largest infarct size and thus the potential benefit of aspirin might be the greatest. Secondly, patients with first anterior AMI have the highest incidence of unfavorable clinical outcome. This is well reflected in the high 3-month mortality (22%) in this trial, which must be due to the entry criteria and the absence of an age limit.

The optimal dosage of aspirin as an antithrombotic agent is still under debate. The dose of 160 mg/day in the International Study of Infarct Survival trial-2 proved to be effective and 100 mg/day decreases the incidence of occlusion of bypass grafts¹⁶ and reperfused

coronary arteries.⁸ Furthermore, a single oral dose of 20 mg aspirin decreases plasma thromboxane levels significantly within 5 minutes.¹⁷ It is unlikely that the dose of aspirin in this trial, though effective for the prevention of reinfarction, was too low to influence infarct size.

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Beneficial Effect of Magnesium Sulfate in Acute Myocardial Infarction

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The effects of magnesium on the incidence of arrhythmias and on mortality were evaluated in 103 patients with documented acute myocardial infarction (AMI) in a randomized, double-blind, placebo-controlled study. Fifty patients received a magnesium infusion for 48 hours and 53 received only the vehicle (isotonic glucose) as placebo. The baseline characteristics of the population were similar in the 2 groups. Tachyarrhythmias requiring drug therapy were recorded in 32% of the patients in the magnesium group and in 45% of the placebo group. Conduction disturbances were found in 23% of the placebo group as compared to 14% in the magnesium group. The intrahospital mortality was 2% (1 patient) in the magnesium group, compared to 17% (9 patients) in the placebo group ($p < 0.01$). No adverse effects were observed during and after the magnesium infusion. These data support a possible protective role of magnesium in patients with AMI.

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Hypomagnesemia was shown to be associated with cardiac arrhythmias,¹⁻⁹ sudden cardiac death from coronary artery disease^{10,11} and recently with increased mortality in acute myocardial infarction (AMI).¹² Furthermore, low levels of magnesium were found in myocardial tissue obtained at necropsy from patients with AMI.^{13,14} The disturbance in magnesium metabolism thus occurs during the acute phase of the AMI, where a high incidence of life-threatening arrhythmias and a high rate of mortality co-exist.^{3,12,14} The serum levels obtained in patients with AMI who survived were either low or normal.^{3,15-17}

While the metabolism of magnesium in AMI and the incidence of arrhythmias were the topics of interest in many studies,¹⁻⁹ only sporadic efforts were made to evaluate the therapeutic potential of magnesium administration to high-risk patients. Rasmussen et al¹² have shown a decrease in mortality and a decrease in the incidence of serious arrhythmias in AMI patients who received intravenous magnesium chloride on hospital admission. We therefore performed a placebo-controlled, double-blind study in 103 consecutive patients with AMI who were randomized to either a magnesium infusion or to placebo for 48 hours. The incidence of arrhythmias and of congestive heart failure was recorded and intrahospital mortality determined.

METHODS

One-hundred fifteen consecutive patients hospitalized with the admission diagnosis of AMI were randomized to either magnesium or placebo groups as soon as possible after admission. Medication was thus started 5.3 ± 3.2 hours (\pm standard deviation) after onset of pain. Fifty-nine patients received continuous magnesium infusion for 48 hours and 56 received placebo (isotonic glucose). Of the 115 patients, 103 were eventually proven to have had a definite AMI according to symptoms, electrocardiographic findings and serum enzymes elevation (all 3 criteria had to be present) and were finally included in the study. Patients were excluded from randomization if circulatory shock or complete bundle branch block or advanced atrioventricular block were present on admission. The randomized patients did not receive prophylactic antiarrhythmic therapy. Thrombolytic therapy was not routinely available at the time of the study. The baseline characteristics of these patients are listed in Table I.

Chi-square test was used for statistical analysis.

Study medication: The patients received 22 grams (91.6 mmol) of magnesium sulfate dissolved in 500 ml

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of isotonic glucose during the first 48 hours, or placebo (500 ml of isotonic glucose). The infusion rate was adjusted so that 6 grams of magnesium were given during the first 3 hours, 10 grams were given during the next 21 hours and 6 grams were given during the last 24 hours. The placebo group patients received equivalent volumes of 5% glucose. During the first 7 days, all patients were monitored electrocardiographically by trained coronary care nurses. In addition, the patients' rhythm was continuously recorded by a computerized Holter system (COMPAS Cardiac Care Units, Inc.) for the first 48 hours. All arrhythmias were recorded and every hour a rhythm strip was obtained and subsequently evaluated by a physician. Blood samples for the determination of magnesium, calcium, potassium, sodium, chloride, phosphorus, whole blood count and cardiac enzymes were obtained on admission and every day for the first 5 days. Serum magnesium concentration was determined by atomic absorption spectrophotometry.¹⁸

RESULTS

Fifty patients with proven AMI received magnesium compared to 53 patients who received isotonic glucose (Table I). The 2 groups were similar in age (although there were more men in the placebo group than in the magnesium group), in average time from onset of chest pain to initiation of treatment, and in prevalence of risk factors (Table I).

The initial levels of magnesium before the beginning of the study (Table II) were normal and there was no significant difference between the 2 groups. As expected, we found an increase in the serum magnesium concentration in the samples taken from the patients of the magnesium group 24 hours after the beginning of the treatment and this level decreased gradually after cessation of the magnesium infusion. The magnesium levels in the placebo group remained steady. In addition, we did not observe initial significant differences in the serum magnesium of survivors and nonsurvivors. There was also no difference in the serum levels of the other electrolytes between patients who died or survived in the 2 groups during the study. No adverse effects of the intravenous magnesium administration were observed.

Clinical course and mortality: Relevant clinical data are listed in Table III. Twenty-four patients (45%) from the placebo group had arrhythmias requiring therapy, compared to only 16 patients (32%) in the magnesium

TABLE I Study Population

	Placebo (%)	Magnesium (%)
Total no. of patients	53	50
Age (yrs \pm SD)	63 \pm 11	64 \pm 10
Men	39 (74)	29 (58)
Age (yrs \pm SD)	62 \pm 12	62 \pm 8
Women	14 (26)	21 (42)
Age (yrs \pm SD)	65 \pm 7	65 \pm 13
Time from pain to treatment (hours \pm SD)	5.4 \pm 3.0	5.3 \pm 3.3
Systemic hypertension (by history)	15 (28)	23 (46)*
Diabetes mellitus	11 (21)	10 (20)
Hyperlipidemia (by history)	6 (11)	2 (4)
Cigarette smokers (>20/day)	18 (34)	15 (30)
Angina pectoris	15 (28)	12 (24)
Previous AMI	11 (21)	6 (12)
Previous diuretic treatment	4 (8)	7 (14)
Anterior (Q wave) myocardial infarction	15 (28.3)	25 (50)

* $p = 0.06$

AMI = acute myocardial infarction; SD = standard deviation.

group ($p = 0.19$). Twelve patients (23%) who received placebo had conduction disturbances during the study, compared to 7 patients (14%) who received magnesium ($p = 0.24$). There was no difference in the number of patients with congestive heart failure during the study in both groups. The difference in mortality between the 2 groups, 17% in the placebo group compared to 2% in the magnesium group, reached a statistically significant level ($p = 0.01$). During the hospital course, 10 patients died, of whom 9 received placebo and 1 received magnesium. Three patients (61 to 85 years old) who received placebo died from electromechanical dissociation between days 1 to 8 and 6 patients (64 to 76 years old) died from cardiogenic shock between days 1 to 4. In the magnesium group, 1 patient (76 years old) died from cardiogenic shock on day 7. History of previous myocardial infarction was obtained in 2 of 9 placebo patients who died.

DISCUSSION

Arrhythmias of all kinds were observed in 24 of 53 (45%) patients receiving placebo and in 16 of 50 (32%) patients receiving magnesium ($p = 0.19$). During AMI, the incidence of conduction disturbances and of congestive heart failure was basically similar in the 2 groups (Table III). The striking finding in our study was the higher mortality in the placebo group (9 deaths vs only 1 in the magnesium group). While the difference

TABLE II Mean Serum Magnesium Concentrations in All 103 AMI Patients (Mean \pm Standard Deviation)

Day	Placebo Group			Magnesium Group	
	All Patients	Survivors	Nonsurvivors*	All Patients	1 Nonsurvivor
1†	1.96 \pm 0.17	1.97 \pm 0.15	1.97 \pm 0.15	2.06 \pm 0.33	1.70
2	1.98 \pm 0.16	1.97 \pm 0.15	2.00 \pm 0.15	3.35 \pm 0.60	3.30
3	2.04 \pm 0.24	2.02 \pm 0.24	2.14 \pm 0.15	3.01 \pm 0.68	2.75
4	2.11 \pm 0.22	2.10 \pm 0.22	2.20 \pm 0.17	2.39 \pm 0.56	2.10
5	2.10 \pm 0.18	2.11 \pm 0.17	2.18 \pm 0.30	2.25 \pm 0.56	2.00

* The numbers were 3 patients on day 1, 6 patients on days 2, 3 and 4, and 4 patients on day 5; † before starting the study medication.

TABLE III Incidence of Arrhythmias (All Types*), Conduction Disturbances, Heart Failure and Mortality in 103 Patients with Acute Myocardial Infarction

	Placebo (%)	Magnesium (%)
Total no. of patients	53 (100)	50 (100)
Severe arrhythmias	24 (45)	16 (32)
Conduction disturbances	12 (23)	7 (14)
Heart failure	13 (26)	13 (28)
Hospital mortality	9 (17)	1 (2) [†]

* Severe arrhythmias were ventricular tachycardia, ventricular fibrillation and ventricular premature beats Low grade 2 to 5; [†] p < 0.01.

reached statistical significance, the relatively small number of patients (103 in both groups) does not totally preclude a possible bias. Thus, there were 21% of patients with previous AMI in the placebo group, compared to 12% in the magnesium group. On the other hand, there was a slight excess of systemic hypertensive patients in the magnesium group, as well as more women and more patients with anterior wall AMI, a slight bias that might have adversely affected the magnesium group.

Rasmussen et al.¹² reported mortality of 7% in patients with AMI who received magnesium compared to 19% of the placebo group. The randomization process, however, was slightly biased favorably toward the magnesium group in their data. Our data strongly support the trend described by Rasmussen et al.¹²

Careful evaluation of the mode of death revealed that most of the mortality in the placebo patients was due to cardiogenic shock or sudden electromechanical dissociation (possible rupture of the left ventricle). The absence of arrhythmic death and the small difference in the incidence of arrhythmia between the groups is not surprising as proper antiarrhythmias therapy was promptly initiated whenever indicated. Thus, the major difference in mortality was due solely to hemodynamic factors and we would not support the theory that the favorable effect of intravenous magnesium therapy in AMI is directly related to its antiarrhythmic effect.^{12,19,20} Although the intravenous administration of magnesium sulfate probably prevents postinfarction hypomagnesemia, we could not document an initial hypomagnesemia (Table II) and thus predict the need for magnesium supplementation. Nevertheless, necropsy studies^{13,14} have shown low levels of magnesium in the infarcted tissue, although the tissue content of magnesium did not always correlate with the serum level.^{21,22} For this reason, studies carried out on lymphocyte levels of magnesium in AMI might be of practical interest.^{22,23} The mechanism of the protective effect of magnesium, therefore, could not be elucidated by our data. A possible myocardial protection, however, must be postulated to explain such a favorable effect on survival in AMI. Several studies have shown possible mechanisms for the cardioprotective effects of magnesium. Thus, magnesium supplementation has been found to decrease the size of myocardial infarction,²⁴ decrease platelet ag-

gregation,²⁵⁻²⁷ decrease basal tension of the arterioles, decrease peripheral vascular resistance and increase coronary vasodilatation.²⁸ Magnesium is also a calcium antagonist, possibly due to its structural similarity as a divalent cation.^{29,30} It remains unclear whether the cardioprotective effect of magnesium supplementation in patients with AMI is due to a correction of a hypomagnesemic state or to the increase of magnesium to above normal levels. Either way, a rapid intravenous administration could have a cardioprotective effect, decrease the myocardial injury and therefore improve immediate survival.

This study was completed before the routine initiation of thrombolytic therapy in our cardiac care unit. However, in respect to its potential for decreasing the immediate mortality from AMI, it appears that this inexpensive, safe and simple therapy should be considered as yet another tool in protecting patients with AMI.

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Effect of Dipyridamole at the Usual Oral Dose on Exercise-Induced Myocardial Ischemia in Stable Angina Pectoris

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A randomized, double-blind, placebo-controlled study was performed to investigate the effect of dipyridamole at a usual oral dose of 150 mg/day on 18 patients with angina pectoris and positive treadmill exercise electrocardiography. After their angina pectoris was stabilized in phase 1, the patients were randomly assigned to sequence group A or B. Group A received a placebo 3 times daily in phase 2 and then 50 mg of dipyridamole 3 times daily in phase 3. Group B received the treatment in the reverse order. The degree of ST depression and the threshold for angina pectoris in treadmill exercise electrocardiography, which was performed on the last days of phases 2 and 3, were compared. The mean duration of exercise was 5 minutes and 23 seconds during dipyridamole and 5 minutes and 13 seconds during placebo administration, with no significant difference. Dipyridamole caused an aggravating effect on the ST change (earlier appearance of ST depression and/or deeper total sum of ST depression at the end of the exercise) in 3 patients, a salutary effect in 5 and no effect in 10. Dipyridamole decreased the threshold for angina pectoris in 5 patients, increased it in 6 and did not change it in 7. To summarize, dipyridamole showed adverse effects (aggravating effects on the ST change and/or on the threshold for angina pectoris) in 6 patients, beneficial effects in 8 and no effect in 4. A usual oral dose of dipyridamole induced myocardial ischemia during exercise in some patients while it improved it in a similar number of patients.

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Dipyridamole, an antiplatelet agent, is reported to prevent coronary events significantly in patients with coronary artery disease.¹ In Japan, this drug is usually administered orally at a dose of 150 mg/day to patients with angina pectoris. However, as illustrated by its intravenous administration in stress testing for ischemic heart disease, a large dose of dipyridamole has been shown to induce myocardial ischemia in patients with coronary artery disease by dilating resistance vessels.² To clarify whether or not dipyridamole at an oral dose of 150 mg/day induces myocardial ischemia in angina patients, we carried out the following double-blind study.

METHODS

The study group comprised 18 patients with typical stable effort angina who exhibited horizontal or down-sloping ST depression of ≥ 0.1 mV on treadmill exercise electrocardiography. Of these patients, 4 had post-myocardial infarction angina and 5 showed stabilization of the condition after admission with unstable angina. The study group was made up of 13 men and 5 women with a mean age of 62 years (range 43 to 72). All patients received calcium antagonists, β blockers or nitrates.

This crossover study was double-blind, placebo-controlled and randomized. The experimental protocol extended over 4 to 6 weeks and was divided into 3 phases, as shown in Figure 1. In phase 1 (2 to 4 weeks), 18 patients underwent a complete clinical evaluation encompassing their history, physical examinations, electrocardiography and treadmill exercise tests. After their angina pectoris had been completely stabilized with antianginal agents, the patients were randomly assigned to sequence group A or B. Group A received a placebo 3 times daily during phase 2 and then 50 mg dipyridamole (Persantine®, Nippon Boehringer Co.) 3 times daily during phase 3. Group B received the same treatment in the reverse order. The medications given at phase 1 were not changed during phases 2 and 3. All patients were permitted to use sublingual nitroglycerin tablets for anginal attacks, but no other medications were added.

Treadmill exercise tests were carried out using a computer-assisted treadmill system (Fukuda Denshi Co.) on the last days of phases 2 and 3. The exercise tests in both phases were performed at the same time in the afternoon using the Bruce protocol. The endpoint of the exercise was taken as the appearance of strong subjective symptoms or a marked ST depression, attainment of the predicted maximal heart rate for the pa-

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tient's age or the development of dyspnea or leg fatigue that prevented continuation of the exercise. In exercise electrocardiography, 15 beats were averaged for the records from leads I, II, aVF, V₁, V₅ and V₆ to eliminate the effects of physical movements on the electrocardiography. The time until the appearance of ST depression of ≥ 0.1 mV in any of the 6 leads and the total sum of the ST depression (Σ ST) in these 6 leads at the endpoint of exercise were compared. When the duration of exercise differed by ≥ 1 minute between phases 2 and 3, Σ ST was compared at the endpoint of the shorter exercise duration. Changes in the time until the appearance of ST depression by ≥ 1 minute and those in Σ ST of ≥ 0.15 mV between the 2 phases were regarded as significant and each change was evaluated as an improvement or deterioration. Changes in the arginal symptoms during the exercise electrocardiography were classified into the 3 categories of no symptoms, chest oppression and chest pain in the order of mild to severe and the time of their appearance and their severity were studied. Changes in the time until the appearance of symptoms by ≥ 1 minute and those in the severity of symptoms by ≥ 1 category at the end of the exercise were regarded as significant. The condition was considered to have deteriorated or improved when at ≥ 1 of these indexes revealed deterioration or improvement as compared with the placebo phase. Coronary angiography was performed in all 18 patients within 1 month before and after the study and the results were evaluated according to the American Heart Association criteria. Stenosis of $\geq 75\%$ was regarded as significant.

RESULTS

Table I lists the results of the treadmill exercise test in all patients. The mean duration of exercise was 5 minutes and 23 seconds during dipyridamole administration and 5 minutes and 13 seconds during placebo administration, with no significant difference. The mean time at onset of ischemic ST-segment depression of ≥ 1 mm in any lead was 2 minutes and 58 seconds \pm 1 minute and 2 seconds during dipyridamole administration and 2 minutes and 50 seconds \pm 1 minute and 4 seconds during placebo administration, with no significant difference. However, ST depression was observed in dipyridamole administration sooner than during placebo administration by ≥ 1 minute in 2 cases and later by ≥ 1 minute in 2 cases. The total sum of the ST depression (Σ ST) at maximum loading was 5.8 ± 2.0

mm during dipyridamole administration and 6.4 ± 2.4 mm during placebo administration, with no significant difference in the mean value, but it increased in 3 cases and decreased in 5 cases during dipyridamole administration as compared with placebo administration. The double product at this time was $17 \times 10^3 \pm 4 \times 10^3$ mm Hg rate/min during dipyridamole administration and $16 \times 10^3 \pm 3 \times 10^3$ mm Hg rate/min during placebo administration, with no significant difference. Thus, the changes in ST depression in exercise electrocardiography were greater during dipyridamole administration in 4 cases and during placebo administration in 5 cases. The symptoms of angina pectoris deteriorated (appeared sooner or were of stronger severity) in 5 patients and improved in 6 patients during dipyridamole administration as compared with placebo administration. To summarize, dipyridamole exerted adverse effects on the induction of myocardial ischemia during exercise in 6 patients (3 in group A and 3 in group B), beneficial effects in 8 patients (4 in group A and 4 in group B) and no effect in 4 patients (3 in group A and 1 in group B).

Coronary angiography revealed 3-vessel disease in 6 patients, 2-vessel disease in 3 patients and 1-vessel disease in 9 patients. Among the 6 patients in whom dipyridamole promoted the development of ischemia, 3-vessel disease was observed in 3 (50%), 2-vessel disease in 1 (17%) and 1-vessel disease in 2 (33%), but in the 8 patients where dipyridamole prevented ischemia, 3 (38%) had 3-vessel disease and 5 (62%) had 1-vessel disease; there was no clear difference in the number of vessels involved between the 2 groups.

DISCUSSION

Dipyridamole is known to aggravate the symptoms of angina pectoris occasionally, but, to our knowledge, there have been no reports suggesting that usual oral doses of dipyridamole may have adverse effects in a considerable percentage of patients, as indicated in this study. The clinical effects of dipyridamole on angina pectoris were examined by several investigators before 1970, but the agent was found to be effective by some,³ while no benefit could be shown by others.⁴ In a Persantine-aspirin reinfarction study, in which the antiplatelet effect of dipyridamole was evaluated, no difference in the frequency of symptoms such as chest pain was observed between the treated and untreated groups.¹ More recently, Loeb et al⁵ found that a single oral administra-

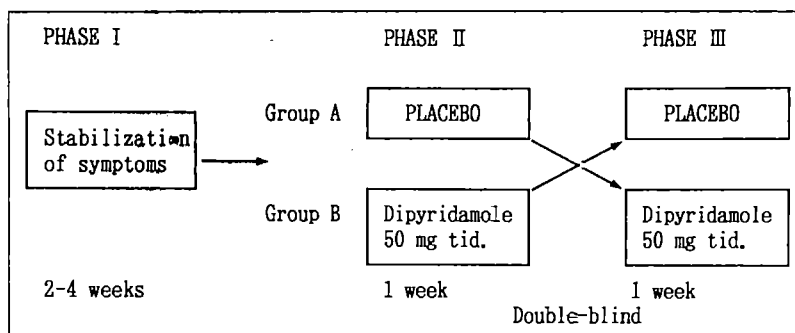


FIGURE 1. Study design.

TABLE I Results of Study

Case	Age (yr) & Sex	AP Only After MI	Exercise Time		Time at Onset of ST Depression		2 ST (mm) at End of Ex		Double Product at End of Ex ($\times 10^3$)		ST Depres- sion of Ex	Change of Angina Pectoris	Diameter Stenosis of Coronary Artery (%)			C
			Dip	P	Dip	P	Dip	P	Dip	P			Right	LAD	LC	
1	60,M	+	2 min 49s	3 min 7s	1 min 31s	1 min 1s	10.0	8.5	16	17	D	D	100	99	99	+
2	71,F	0	6 min 0s	6 min 7s	3 min 6s	3 min 23s	4.5	3.0	12	12	D	D	99	90	90	+
3	64,M	0	2 min 37s	3 min 0s	3 min 6s	4 min 54s	5.0	4.5	22	20	D	D	75	99	99	0
4	54,M	+	6 min 50s	6 min 28s	1 min 6s	5 min 18s	6.0	3.5	12	13	D	D	0	90	0	0
5	69,M	0	7 min 13s	7 min 25s	3 min 23s	3 min 0s	5.0	5.5	18	19	0	D	50	99	0	0
6	56,M	0	4 min 49s	6 min 0s	3 min 19s	2 min 22s	6.5	7.5	17	17	0	D	90	75	0	+
7	61,F	0	6 min 11s	5 min 6s	3 min 5s	3 min 6s	8.0	10.0	22	21	0	0	0	75	0	0
8	43,M	0	12 min 0s	8 min 32s	5 min 31s	4 min 23s	6.5	10.5	19	16	0	0	0	75	0	0
9	63,F	0	3 min 58s	3 min 13s	2 min 26s	1 min 47s	5.0	7.5	17	17	0	0	75	90	75	0
10	67,M	+	7 min 43s	8 min 42s	2 min 21s	2 min 15s	4.5	7.5	21	18	0	0	100	90	99	+
11	59,M	0	6 min 45s	5 min 0s	4 min 48s	2 min 57s	3.0	5.0	16	22	0	0	90	100	0	+
12	59,M	0	6 min 36s	6 min 29s	2 min 52s	2 min 1s	5.0	5.5	21	20	0	0	0	50	0	+
13	67,M	0	4 min 18s	4 min 10s	1 min 24s	1 min 31s	7.5	8.5	15	16	0	0	100	99	0	+
14	71,M	+	4 min 11s	4 min 30s	1 min 13s	2 min 37s	6.0	6.5	12	11	0	0	0	99	90	+
15	54,M	0	4 min 30s	4 min 36s	1 min 59s	2 min 53s	9.5	10.0	13	15	0	0	0	0	99	+
16	72,F	0	3 min 0s	2 min 23s	2 min 4s	1 min 45s	5.5	5.5	22	15	0	0	0	99	0	+
17	56,M	0	3 min 23s	5 min 13s	3 min 16s	3 min 13s	1.5	2.5	12	10	0	0	50	99	100	+
18	64,F	0	4 min 0s	5 min 13s	2 min 35s	3 min 37s	4.5	4.5	17	17	0	0	0	100	0	+
Mean	62		5 min 23s	5 min 13s	2 min 58s	2 min 50s	5.8	6.4	17	16						
SD	7		2 min 14s	1 min 47s	1 min 2s	1 min 4s	2.0	2.4	4	3						

AP = angina pectoris; C = collateral; D = deterioration; Dip = dipyridamole; Double product = systolic blood pressure (mm Hg) \times (rate/min); Ex = treadmill exercise; I = improvement; LAD = left anterior descending artery; LC = left circumflex artery; MI = myocardial infarction; P = placebo; SD = standard deviation; ST = total sum of ST depression in 6 leads (I, II, aVL, V₁, V₅, V₆).

tion of 150 mg dipyridamole did not affect the threshold of anginal symptoms in an atrial pacing study.³ Our results are considered different from these earlier reports, because we examined the effects of dipyridamole according to the improvement or deterioration of ST depression and anginal symptoms during treadmill exercise tests rather than by statistical analysis of changes in the frequency of attacks or changes in the tolerance against exercise.

Dipyridamole dilates the coronary artery and increases coronary blood flow. However, this agent, which dilates resistance vessels instead of conductance vessels, has been experimentally proven to induce myocardial ischemia by the following mechanism. An increase in flow of the stenotic artery causes a greater pressure decrease across the stenosis, resulting in a decrease in the coronary driving pressure. This decrease in driving pressure is not accompanied by a decrease in resistance of the subendocardial vessels since the latter are already maximally dilated. This causes a decrease in the subendocardial blood flow.⁶ When the stenosed artery provides collaterals to the ischemic region, a decrease in the collateral driving pressure leads to aggravation of ischemia.⁷ Clinically, Gould et al² showed that intravenously administered dipyridamole at a dose of 0.142 mg/kg induced ischemia in the presence of coronary stenosis also in humans.² However, the blood concentration of dipyridamole after oral administration of 150 mg/day (0.8 to 1.4 $\mu\text{g/ml}$)⁸ is about one-fourth of that after intravenous administration of 0.142 mg/kg ($4.6 \pm 1.3 \mu\text{g/ml}$).⁹ The strength of the coronary dilator effect of dipyridamole at this concentration and whether it induces or prevents myocardial ischemia remain to be clarified. However, the coronary lesions among individual cases are extremely diverse and oral administration of dipyridamole at 150 mg/day may promote myocardial ischemia in some patients, but prevent it in others.

This study had several limitations. First, the number of patients in the study was small and patients with severe angina accounted for a relatively high percentage. Therefore, whether these patients were representative of the anginal population to which dipyridamole is administered in Japan is questionable and the results are not conclusive. However, for the purposes of this preliminary study aimed at evaluating the effects of oral administration of 150 mg/day dipyridamole in anginal patients, the number of patients was considered appropriate. Second, since administration of antianginal drugs other than dipyridamole was maintained during the study, their possible effects on the results cannot be ignored. Administration of these antianginal drugs could not be suspended, because anginal attacks had just disappeared or become stabilized under these treatments. Nevertheless, considering the fact that dipyridamole is seldom used alone in anginal patients, examination of its effects during concomitant administration of other drugs may be truer to the conditions of its actual use.

Third, according to the protocol of this study, both dipyridamole and placebo were administered only for 1 week. This was because of the following reasons: long-standing administration of a drug that might have adverse effects on angina pectoris was considered undesirable in a double-blind trial; and short-term administration was considered to suffice for producing changes in the results of the exercise test, if not the frequency of attacks. We considered that the blood level of dipyridamole would be stabilized after 1-week oral administration and that the drug would be sufficiently washed out during the 1-week withdrawal. Fourth, we evaluated the effects of dipyridamole according to the changes in ST on exercise electrocardiography and anginal symptoms during the exercise test. The validity of our assumption that changes in ST of ≥ 1.5 mm and in the time of the onset of anginal symptoms by ≥ 1 minute are significant must be tested further. Although the effects of day-to-day variations cannot be excluded, dipyridamole at a daily dose of about 150 mg appears to produce both beneficial and adverse effects, depending on the individual case, and, in order to evaluate such effects, this protocol is considered to be needed.

The results of this study were not conclusive as to whether dipyridamole is beneficial or harmful for angina patients. However, based on the finding that dipyridamole induced myocardial ischemia during the treadmill exercise test in many patients while it improved myocardial blood flow in a similar number of patients, the drug should be used carefully in patients considered to have severe coronary stenosis, closely monitoring its effects on the ST changes and symptoms during the treadmill exercise test. More detailed studies involving a larger series of patients need to be undertaken for further evaluation of this problem.

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Reduction of Myocardial Ischemia During Percutaneous Transluminal Coronary Angioplasty with Oxygenated Fluosol®

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The effects of perfusion of an oxygen-carrying perfluorochemical emulsion (Fluosol®) in alleviating symptoms of myocardial ischemia during balloon occlusion were examined in a multicenter trial of 245 patients. Severe anginal pain occurred less frequently in patients receiving Fluosol perfusion (21%) than in those receiving routine angioplasty (34%) ($p < 0.05$). ST-segment changes at balloon deflation in routine angioplasty patients were significantly greater than in patients who received oxygenated Fluosol perfusion (2.2 ± 1.2 vs 1.7 ± 0.9 mm; $p < 0.03$). Profound regional wall dysfunction (-561 ± 224 U) was observed in routine angioplasty patients by 2-dimensional echocardiography. Patients receiving oxygenated Fluosol perfusion, however, maintained near baseline levels of ventricular function (-61 ± 335 U) during occlusion ($p < 0.0001$). Mean global left ventricular ejection fraction was preserved at baseline levels during balloon inflation in patients perfused with oxygenated Fluosol but decreased significantly ($p < 0.001$) during occlusion in routine angioplasty patients. A total of 26 complications (19 routine group; 7 per-

fusion group) was reported. Adverse responses to the perfusate were infrequent, occurring in 1.6 and 2.0% of patients after the test dose and during perfusion, respectively. Thus, transcatheter perfusion with an oxygen-carrying perfluorochemical emulsion is effective in alleviating myocardial ischemia during angioplasty and can be safely administered in this patient population.

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Balloon inflation accompanying percutaneous transluminal coronary angioplasty (PTCA) interrupts coronary blood flow, resulting in myocardial ischemia.¹⁻⁴ For short balloon inflations, the physiologic effects of ischemia, ventricular dysfunction, electrical instability and chest pain may be clinically tolerable because they usually resolve rapidly after balloon deflation. However, patients with limited contractile reserve because of previous myocardial infarction or with large regions of myocardium jeopardized by PTCA of proximal sites may experience marked hemodynamic and electrical instability during balloon occlusion.² Further, prolonged balloon inflations may increase the effectiveness of PTCA,⁵ when balloon inflation leads to poor angiographic results and inadequate restoration of flow after balloon deflation; however, repeated or prolonged inflations may produce some functional impairment, which is only slowly reversible.⁶ The perfluorochemical emulsion Fluosol® (20% intravascular perfluorochemical emulsion, Alpha Therapeutic Corp.) is an acellular fluid with high oxygen-carrying capacity, a viscosity approximately half that of whole blood and a small particle size ($0.270 \mu\text{m}$).⁷ Perfusion of this emulsion through the central lumen of the balloon catheter into the distal coronary bed permits preservation of adequate tissue oxygenation and ameliorates deleterious effects of ischemia.⁸⁻¹⁰ The purpose of this study was to extend these initial clinical observations to a larger population in this multicenter trial to evaluate the ability of oxygenated Fluosol perfusion during balloon occlusion to mitigate intraprocedural ischemia.

METHODS

Study design: The study was a randomized, double-blind multicenter trial with 10 participating hospitals,

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located at the University of California at Los Angeles, Mount Sinai/University of Wisconsin, St. Vincent, Georgetown University, Sequoia Hospital, Vanderbilt University, Medical College of Virginia, Yale-New Haven Hospital, Veterans Administration Medical Center and Emory University. Patients were randomized to receive either routine PTCA with no perfusion of any agent or PTCA with transcatheter coronary perfusion of oxygenated Fluosol at 60 ml/min distal to the inflated balloon. Patients were randomized before the PTCA procedure after informed consent was obtained. During all procedures, the infusion pump was loaded with oxygenated Fluosol and connected to the lumen of the balloon catheter. Neither the patient nor the physician knew whether the infusion pump was turned on. Only 1 stenosis/patient was treated under study conditions, although additional lesions may have been dilated during a given patient's procedure. The lesion treated under study conditions was that which was felt to jeopardize flow to the largest amount of myocardium. Patients randomized to the treatment group underwent an initial inflation without perfusion to provide baseline electrocardiographic measurement and 2-dimensional echocardiographic functional assessment.

Patient population: Patients were >18 years of age, undergoing elective coronary angioplasty with reversible myocardial ischemia due to single or multivessel coronary artery disease involving the left anterior descending, right or circumflex artery. Exclusion criteria were angiographically visible collaterals, lesions involving a major side branch, a severe lesion distal to the treated lesion that could prevent adequate perfusion, pregnancy, dialysis, liver disease, a stenosis of a bypass conduit, recent myocardial infarction, congestive heart failure or left bundle branch block. Studies were undertaken after approval of the human research review committee at each respective institution. Patients were withdrawn from the trial if their procedures required use of a balloon catheter without a central lumen adequate for perfusion.

Perfusate: Fluosol was oxygenated to a pO_2 of >600 mm Hg by bubbling with a gas mixture of 95% oxygen/5% carbon dioxide at approximately 2 liters/min for at least 30 minutes. The fluid was warmed to 37°C before administration. Oxygenated Fluosol was perfused through the central lumen of the balloon catheter with the guidewire in place into the coronary artery distal to the balloon occlusion at 60 ml/min using a MedRad Mark IV injector (MedRad Inc.) with the warming mantle in place to maintain perfusate temperature.

Before angiography, a test dose of 0.5 ml of Fluosol or saline was administered intravenously to patients randomized to receive Fluosol perfusion and routine PTCA, respectively. Vital signs and subjective responses were monitored for 10 minutes.

Angioplasty procedure: Angioplasty was performed using USCI (C. R. Bard, Inc.) or Advanced Cardiovascular Systems, Inc. balloon catheters through which pressure gradients could be measured with the guidewire (usually 0.014 inches) in place, of 2.0 to 4.0 mm diameter, with 3.0 mm used most frequently in both groups. The catheters used varied during the time peri-

od of the study, from 1985 to 1987 (e.g., Delta, Profile Plus, LPS).

Electrocardiograph: Electrocardiographic data were recorded for each patient on a continuous 3-channel Holter monitoring system (Scole Engineering Co.) during the procedure using a V_5 , aVF and modified V_2 radiolucent bipolar lead system.¹¹ Tapes were analyzed at a central site (Georgetown) using a Marquette 8000 Holter playback computer digitally interfaced to a DEC PDP 11/24 minicomputer (Digital Equipment Corp.). Mean ST-segment deviation, measured 60 ms beyond the J point, was analyzed at 10-second intervals in the lead showing maximal ST-segment deviation. The magnitude of ST-segment deviation from baseline at balloon deflation in all patients who manifested ST-segment change with the nonperfused inflation, the rate of ischemia evolution (ST level divided by time) during early (first 30 seconds) and late (last 30 seconds before deflation) balloon inflation and the rate of ST recovery to baseline after deflation were examined during inflations 2, 3 and 4. Nonsustained (<9 beats/run) and sustained (≥ 9 beats/run) ventricular ectopy were also monitored.

Twelve-lead electrocardiograms were obtained at baseline and 1 day after the procedure. The presence or absence of ventricular premature contractions, Q-waves, T-wave or ST-segment changes and conduction defects were assessed.

Anginal pain: Patients were asked to grade their chest discomfort during angioplasty on a scale of 0 to 9. The time from balloon inflation to onset of angina, duration of angina and the intensity of pain (0 to 9 scale) at 30, 60 and 90 seconds during balloon inflation were recorded. For analysis, pain was classified as mild (1 to 3), moderate (4 to 6) or severe (7 to 9). Data from inflations 2, 3 and 4 were used for analyses.

Quantitative 2-dimensional echocardiography: Continuous 2-dimensional echocardiographic studies acquired simultaneously with balloon inflation were analyzed for a subset of 24 patients (11 routine; 13 perfusion) with predominantly left anterior descending artery lesions (92%) from 4 clinical sites using standard Hewlett-Packard 2-dimensional echocardiographic equipment. Either apical long-axis or 4-chamber views were used to evaluate the anteroapical and anteroapical left ventricular walls. Quantitative analysis was performed in the core laboratory (Yale University), without knowledge of the treatment by a previously described method of Bolson et al.¹² The chord shortening patterns for ≥ 3 beats established baseline mean shortening (± 2 standard deviations) during the preischemic state. Normalized chord shortening units would be positive during normal contraction but become minimal or negative during akinesis or dyskinesis. During the balloon inflation period, the area of excursion of chord shortening outside the ± 2 standard deviations range provided a single overall value encompassing both the severity and extent of ventricular dysfunction during balloon occlusion.

Myocardial wall dysfunction was expressed as the area of dysfunction (summed chord shortening area from the beginning of dysfunction until balloon deflation, expressed in chord shortening area-time units, out-

TABLE I Patient Characteristics

	Routine (n = 106)	Treatment (n = 99)	p Value
Age (yrs)	58 ± 10	57 ± 10	NS
Sex (% male)	72	75	NS
Stable angina (%)	59	58	NS
Duration (mos)	9 ± 13	12 ± 19	NS
Angina class (CHA)			
I	9	6	NS
II	51	48	NS
III	38	35	NS
IV	2	12	0.05
Hypertension (%)	52	39	NS
Diabetes mellitus (%)	11	11	NS
Cigarette smoking (%)	63	66	NS
Prior AMI (%)	31	35	NS
Prior CABG (%)	5	6	NS
Prior PTCA (%)	19	14	NS
Multivessel CAD (%)	50	38	NS
PTCA artery (%)			
LAD	57	50	NS
Right	26	27	NS
Left circumflex	18	23	NS
Mean % stenosis (diameter)	82	79	NS

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHA = Canadian Heart Association; LAD = left anterior descending coronary artery; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

side the ± 2 standard deviations range defined during the preischemic baseline) and peak dysfunction (maximum level of dysfunction below the -2 standard deviations level during balloon inflation, expressed as chord shortening area units). Peak dysfunction, as a negative value, indicates the extent and severity of myocardial hypokinesis or dyskinesis. Temporal variables assessed were: the time to onset of dysfunction (time from balloon inflation until the beginning of sustained wall dysfunction outside the normal ± 2 standard deviations region); time to recovery (time from balloon deflation until the return of ventricular function within the ± 2 standard deviations baseline levels); and time to peak dysfunction (the time from balloon inflation until peak dysfunction).

Global left ventricular ejection fraction was calculated from 2-dimensional echocardiographic data at base-

TABLE II Intraprocedural Electrocardiographic Findings

	Routine (n = 59)	Treatment (n = 36)	p Value
ST level at deflation (mm)	2.2 ± 1.2	1.7 ± 0.9	0.03
Early ST change (mm/s)	0.044 ± 0.025	0.043 ± 0.026	NS
Late ST change (mm/s)	0.031 ± 0.021	0.019 ± 0.023	0.01
Time to 1 mm change (s)	36 ± 17	37 ± 17	NS
Time to recovery (s)	59 ± 36	47 ± 25	0.03

Values are expressed as mean \pm standard deviation. Early ST change is the rate of ST-segment evolution during the first 30 seconds of balloon inflation. Late ST change is the rate of ST-segment evolution after 30 seconds of balloon inflation and before deflation.
NS = not significant.

line and at 45 seconds of balloon occlusion using the single-plane area-length calculation methods of Sandler and Dodge.¹³

Statistical analysis: Statistical significance ($p < 0.05$) for the ST-segment and 2-dimensional echocardiographic variables was determined with the 2-sided t test. Analysis of pain (severe/not severe) was performed using the Pearson chi-square test. For comparisons of demographics and safety variables, a separate t test was used for continuous variables and the Pearson chi-square test (1-tail) was used for categorical variables.

RESULTS

Study population: Of the 245 patients entered into the study, 118 were randomized to receive routine angioplasty and 127 to receive treatment with oxygenated Fluosol perfusion during angioplasty. Forty patients (14 routine; 26 Fluosol PTCA) were withdrawn from the study before assigned treatment. Nineteen had significant angiographic changes between screening and the procedure (10 routine, 9 Fluosol), e.g., development of collaterals, insignificant stenoses or new occlusive disease requiring bypass surgery. In 11 patients the narrowing could not be crossed (2 routine, 9 Fluosol), and in 6 patients, a catheter suitable for perfusion of Fluosol could not be passed across the stenosis (1 routine, 5 Fluosol). In 3 patients, the protocol was cancelled or not completed. Three patients were withdrawn because of adverse responses to the Fluosol test dose (2 patients) or to Fluosol perfusion (1 patient) and 1 patient was withdrawn because of scheduling (excessive time delay). Two patients randomized to receive Fluosol did not get perfusion and were crossed over to the routine group. The final efficacy analysis included 106 patients (104 randomized plus 2 crossovers) who underwent routine angioplasty and 99 patients (101 randomized minus 2 crossovers) who received Fluosol infusion. Baseline clinical profiles of patients randomized to both study groups were similar (Table I).

Procedural variables: Multiple inflations were performed in each patient, and duration ranged from 10 to 250 seconds, with the mean (\pm standard deviation) for routine patients (71.0 ± 24.6 seconds) not differing from that for perfusion patients (72.4 ± 27.7 seconds). Perfusion rates were 1.1 to 3.0 ml/kg of material.

Electrocardiographic results: All 3 channels were felt to be important and were not of satisfactory quality in some patients. Standardized, stable baseline low noise recordings were available in 59 of 106 patients assigned

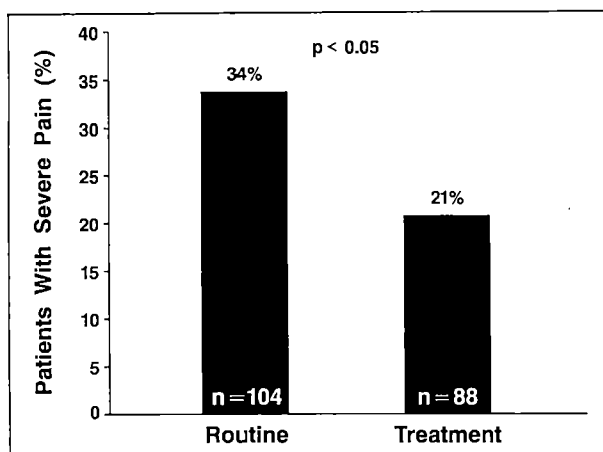


FIGURE 1. Severity of anginal pain during balloon inflation in patients treated with routine angioplasty and angioplasty during transcatheter perfusion of oxygenated Fluosol.

to routine PTCA and 36 of 92 patients who received Fluosol. Tapes were lost because >1 channel was not satisfactory for analysis, bundle branch block developed and tapes were lost in transit. Baseline characteristics and procedural outcome in the patients in whom ST-segment recordings were and were not obtained were not different. ST-segment changes during balloon inflation were observed in both study groups (Table II). However, at deflation, the mean ST-segment level was significantly less in patients with perfusion. Over the first 30 seconds of inflation, ST-segment changes evolved at a similar rate in both groups. However, after 30 seconds of inflation, the rate of evolution of ST-segment changes was significantly slower with perfusion than routine. The time to recovery to baseline levels after balloon deflation was shorter in Fluosol patients.

Anginal pain: The proportion of patients reporting severe pain was 34% in patients randomized to routine angioplasty in contrast with only 21% ($p < 0.05$) in patients treated with Fluosol (Figure 1).

Two-dimensional echocardiographic data: In patients randomized to routine nonperfused angioplasty, a reproducible pattern of profound left ventricular dysfunction was observed in all patients studied, as well as decreased regional ventricular chord shortening (Table III). In contrast, regional wall function was preserved at or near baseline levels throughout balloon inflation in patients receiving Fluosol perfusion, and maximum dysfunction was greater in routine than Fluosol patients. Figure 2 shows examples of the regional dysfunction observed during balloon occlusion in a routine patient and in a patient with Fluosol perfusion. Six of the 13 patients perfused with Fluosol exhibited no regional ventricular dysfunction during balloon inflation with the overall regional wall function remaining at or above baseline levels.

During balloon inflation, global left ventricular ejection fraction in routine patients declined significantly, but remained at baseline in Fluosol patients (Figure 3).

TABLE III Two-Dimensional Echocardiography

	Routine (n = 11)	Treatment (n = 13)	p Value
Area of dysfunction	-561 ± 224	-61 ± 335	0.0001
Peak dysfunction	-155 ± 45	-48 ± 59	0.001
Time to dysfunction (s)	5 ± 5	11 ± 31	NS
Time to peak dysfunction (s)	36 ± 12	37 ± 31	NS
Time to recovery (s)	48 ± 25	29 ± 18	NS

Values are expressed as mean ± standard deviation. Area of dysfunction expressed in chord shortening area time units; peak dysfunction expressed in chord shortening area units. Data available are for 7 Fluosol-percutaneous transluminal coronary angioplasty patients for temporal variables.

NS = not significant.

Clinical outcome: The clinical cohort was composed of 204 patients. The angiographic diameter of the stenosis was reduced from 82 ± 13 to $24 \pm 16\%$ in patients undergoing routine angioplasty and from 79 ± 13 to $19 \pm 14\%$ in patients receiving Fluosol (difference not significant). A total of 19 complications was reported in the routine treatment group; 7 occurred in the Fluosol perfusion group (Table IV). One patient, randomized to routine angioplasty, died of cardiac arrest during angioplasty. Adverse experiences related to Fluosol administration were uncommon and mild; 2 patients (1.6%) experienced low back pain after the Fluosol test dose and 2 patients (2%) experienced complications during Fluosol perfusion. One patient experienced ventricular fibrillation requiring cardioversion, possibly due to Fluosol perfusion at room temperature. A second patient experienced hypotension, dyspnea and chest pain associated with balloon malfunction from attempts to perfuse through a catheter that could not accommodate the perfusion rate. Increased pressure on the vessel wall may have affected the response. Both patients recovered successfully without long-term residual effects.

Intraprocedural Holter recordings, 12-lead electrocardiograms and creatine kinase values obtained at baseline, immediately after angioplasty and at 8, 16 and

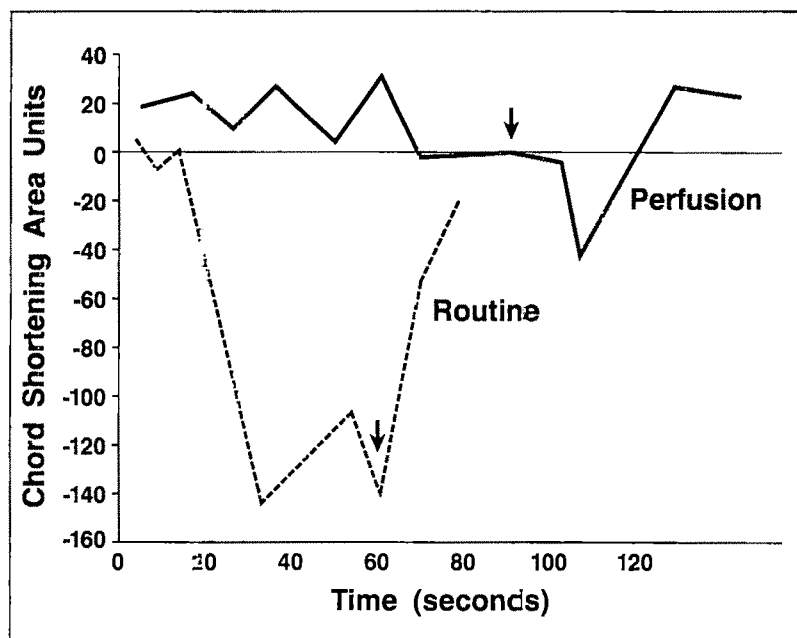


FIGURE 2. Comparison of the time course of regional left ventricular function during balloon occlusion in a routine angioplasty patient and a patient treated with oxygenated Fluosol perfusion. Arrows indicate balloon deflation.

TABLE IV Procedural Complications

	Routine		Treatment		p Value
	No.	%	No.	%	
Abrupt reclosure	4	3.8	0	0.0	NS
Emergency CABG	1	0.9	1	1.0	NS
Myocardial infarction	2	1.9	1	1.0	NS
Arrhythmia requiring therapy	2	1.9	2	2.0	NS
Arrhythmia not requiring therapy	1	0.9	0	0.0	NS
Dissection with occlusion	2	1.9	0	0.0	NS
Spasm requiring therapy	2	1.9	0	0.0	NS
Coronary embolism	0	0.0	1	1.0	NS
Prolonged angina	2	1.9	1	1.0	NS
Hypotension	2	1.9	0	0.0	NS
Ventricular fibrillation	0	0.0	1	1.0	NS
Death	1	0.9	0	0.0	NS
Total	19		7		

CABG = coronary artery bypass graft surgery; NS = not significant.

24 hours after the procedure showed no significant differences between the 2 study groups.

DISCUSSION

Relief of intraprocedural ischemia: This study demonstrates that perfusion of oxygenated Fluosol into the vessel supplying the ischemic myocardium during balloon occlusions of PTCA mitigates the consequences of the regional myocardial ischemia incurred during the procedure. This was manifested by a significant reduction in electrocardiographic and functional parameters of ischemia. Intracoronary administration of Fluosol at a perfusion flow rate of 60 ml/min in total volumes of ≤ 500 ml was well tolerated in this patient population.

The preservation of ventricular function during Fluosol perfusion has been confirmed in other studies.

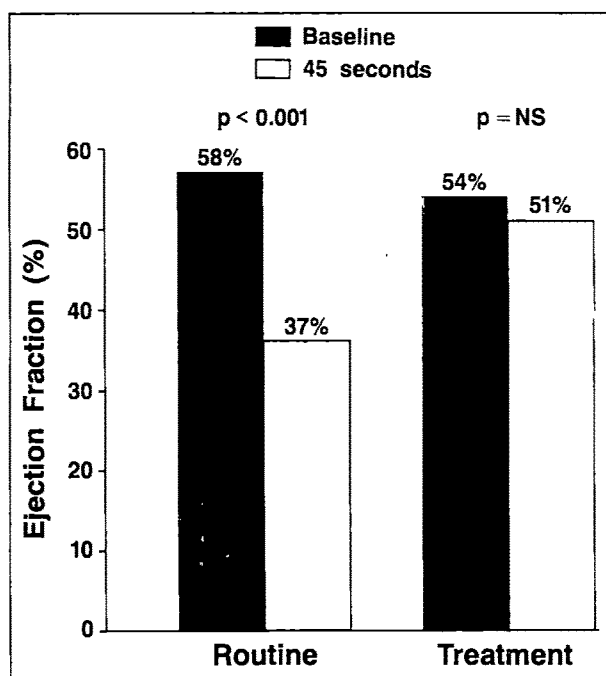


FIGURE 3. Global left ventricular ejection fraction in routine angioplasty patients and patients treated with oxygenated Fluosol perfusion at baseline and after 45 seconds of balloon occlusion. NS = not significant.

Cleman et al⁹ reported preservation of regional chord shortening after 60 seconds of balloon occlusion with oxygenated Fluosol perfusion compared to nonperfused occlusion. Similarly, preservation of global ejection fraction with oxygenated Fluosol perfusion was comparable to routine nonperfused inflations where ejection fraction decreased from a baseline of 57 ± 15 to $36 \pm 14\%$ at 45 seconds of occlusion ($p < 0.0005$).¹⁰

Similar results have been reported using animal models. Virmani et al¹⁴ demonstrated that perfusion of oxygenated Fluosol improved fractional shortening compared to perfusion with oxygenated Ringer's lactate solution or with no perfusion. In a similar study using 2-dimensional echocardiography, Tokioka et al¹⁵ found that ventricular function was improved during perfusion with Fluosol compared to unprotected inflations.

Because of its high oxygen-carrying capacity, perfusion of the ischemic region with oxygenated Fluosol prevents severe tissue hypoxia. Rude et al¹⁶ demonstrated an increase in intramyocardial oxygen tension with intravenous administration of Fluosol during ventilation with 100% oxygen. In another canine model, with perfusion with oxygenated Fluosol at 50 ml/min, there was lactate production in the early reperfusion phase, although levels were less than those observed during routine unprotected occlusions.¹⁵ The failure to preserve lactate metabolism at preocclusion levels may reflect incomplete protection in this model. However, differences in the hyperemic state after perfused and nonperfused inflations may affect lactate mobilization and subsequent measurement. The metabolite washout effects of perfusion alone do not account for the preservation of myocardial function by oxygenated Fluosol. Perfusion with oxygenated Ringer's lactate solution or with un-oxygenated Fluosol failed to preserve mechanical function during balloon occlusion in angioplasty patients.¹⁰

Effect of perfusion on ST-segment changes: Anderson et al⁸ reported a significant reduction of ST-segment response to balloon occlusion during oxygenated Fluosol perfusion compared to Ringer's lactate solution perfusion. In the current study, the similarity of ST-segment evolution rates during the first 30 seconds of balloon inflation in routine and perfused patients suggests that transcatheter perfusion may itself affect the electrical pattern of the myocardium in the absence of ischemia. The effects of transcatheter perfusion alone were examined in animals subjected to open artery (no balloon occlusion) perfusion (3 ml/kg/min) of oxygenated Fluosol and nonoxygenated Ringer's lactate solution. Significant ST-segment elevation mimicking ischemia was observed during perfusion with either perfluorochemical or electrolyte solutions; however, regional left ventricular function remained normal during perfusion. In contrast, during unprotected occlusion, both significant ST-segment elevation and myocardial dysfunction were observed.¹⁴ In the current study, the rate of ST-segment elevation in patients receiving Fluosol perfusion decreased markedly after 30 seconds of inflation.

Safety of administration: A single incidence of ventricular fibrillation occurred when Fluosol was perfused at room temperature. Transcatheter administration of

fluids should be only with fluids at or near 37°. Anderson et al⁸ reported that the rate of pulmonary artery wedge pressure change during transcatheter perfusion was significantly lower during Fluosol administration than during Ringer's lactate solution perfusion.

Role of Fluosol perfusion in angioplasty: The relief of the myocardial ischemia resulting from balloon occlusion during coronary angioplasty Fluosol perfusion may expand the indication for the angioplasty procedure. Recent studies have suggested that prolonged balloon inflation times result in higher primary success rates, and longer balloon inflation times may also favorably affect the recurrence rate.⁵ Prolongation of balloon inflation times using Fluosol may permit examination of this hypothesis. More importantly, increasing numbers of patients with substantial regions of myocardium at risk or limited coronary reserve are undergoing treatment with angioplasty. Administration of oxygenated Fluosol, by alleviating intraprocedural ischemic effects and increasing procedural safety, may be an important adjunctive therapy in these cases.

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Outcome Following Emergency Coronary Artery Bypass Grafting for Failed Elective Balloon Coronary Angioplasty in Patients with Prior Coronary Bypass

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To assess frequency and outcome of emergency coronary artery bypass grafting (CABG) for failed coronary angioplasty in patients with prior CABG, 2,136 elective angioplasty procedures in prior CABG patients were reviewed over a 10-year period. Emergency surgical revascularization was required in 19 patients (0.9%) with prior CABG, compared with 130 of 6,974 patients (1.9%) without prior CABG ($p = 0.001$). The interval from the most recent CABG to the failed coronary angioplasty was 6.8 years (range 1 to 16). Referral for emergency CABG was made on the basis of an acute closure not responding to repeat dilatation in 12 native coronary arteries and in 7 saphenous vein grafts. Severe hemodynamic instability after acute closure required the placement of an intra-aortic balloon pump in 3 patients, including 2 who required cardiopulmonary resuscitation. A total of 34 saphenous vein grafts and 1 internal mammary artery graft were placed emergently. Three patients with high-risk features (3 prior CABG operations in 1 patient, single remaining vessel to heart in 2 patients) could not be weaned from cardiopulmonary bypass. The remaining 16 patients were discharged after a mean hospital stay of 16 days. Four patients developed new Q waves after CABG. At follow-up (mean 52 months, range 3 to 99), 1 patient died late from an acute myocardial infarction. The 15 survivors had no or mild angina and were free of further CABG. Thus, emergency CABG after failed angioplasty in patients with prior CABG is required infrequently. In patients without extreme high-risk features, emergency repeat CABG can be accomplished with good hospital and long-term results.

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In most patients, ischemic symptoms are relieved after coronary artery bypass grafting (CABG). Over time, however, native and graft coronary artery disease progresses, leading to the return of angina in many patients.^{1,2} Repeat surgical revascularization is associated with increased operative morbidity and mortality in most series.³⁻⁶ In contrast, percutaneous transluminal coronary angioplasty is usually associated with low procedural risks and high success rates in patients with prior CABG.⁷⁻¹¹ However, acute occlusion and subsequent ischemic complications after angioplasty may occur in patients with prior CABG in a manner similar to patients with native coronary artery disease.¹² The characteristics and outcome of patients requiring emergency CABG for failed native vessel coronary angioplasty have been reported.¹³⁻²³ This report describes the frequency, characteristics and outcome of patients requiring emergency repeat CABG for failed elective coronary angioplasty over a 10-year period.

METHODS

Patient selection: From 1980 through 1989, 10,000 procedures were performed by our group at the Mid America Heart Institute, including 2,224 in patients with prior CABG (22%). Excluding 88 patients with prior CABG treated with coronary angioplasty for an acute myocardial infarction, 2,136 CABG patients form the study group of elective coronary angioplasty. Failed coronary angioplasty requiring emergency CABG was defined as the occurrence of an acute ischemic complication during the coronary angioplasty procedure leading to the immediate transfer of the patient to the operating room. Patients with unsuccessful but uncomplicated coronary angioplasty referred for elective CABG later in their hospital stay were not included in this analysis.

Angioplasty protocol: Patients received 10,000 U of heparin in the catheterization laboratory. An additional 5,000 U of heparin were given for every hour of the angioplasty procedure. Unless contraindicated, routine premedications consisted of 325 mg aspirin 3 times daily, 75 mg dipyridamole 3 times daily, 5 mg isosorbide dinitrate sublingually, 75 mg lidocaine intravenously, 5 mg verapamil intravenously and 500 cc dextran intravenously. Standard angioplasty guides, catheters and guidewires were used. Gradual balloon inflations were

used with balloon sizes selected to be comparable to the target vessel. After identification of an intimal dissection, prolonged inflations with balloon catheters of a similar or slightly larger size were generally attempted to repair the dissection. Autoperfusion catheters were not available in our early experience, and their use was determined by the individual operator.

Definitions: Significant coronary artery disease was defined as a stenosis of the luminal diameter of a major epicardial coronary artery or a bypass graft of 70% or more. Anginal status was classified according to the New York Heart Association. Periprocedural myocardial infarction was considered "definite" after the development of new significant Q waves (≥ 40 ms duration) on the electrocardiogram, and "probable" after an elevation of creatine kinase enzymes ≥ 500 IU/ml with 10% or more MB isoenzymes in the absence of new Q waves. A patient was designated as having only a single remaining vessel to the heart when all bypass grafts and native coronary arteries were occluded proximally with the exception of 1 remaining arterial conduit supplying all viable myocardium.

Follow-up: Hospital records and subsequent clinical contacts were reviewed for each patient. All surviving patients were interviewed by a physician and, in the event of death, the next of kin were contacted.

Statistics: Results are reported as the mean \pm 1 standard deviation. Categorical variables were compared using Fisher's exact test. A p value < 0.05 was considered significant.

RESULTS

Clinical characteristics: During the study period, 19 of 2,136 (0.9%) patients with prior CABG were referred for emergency repeat CABG. During the same period 130 of 5,974 (1.9%) patients without prior CABG undergoing elective coronary angioplasty required emergency CABG ($p = 0.001$). The frequency of referral of patients with prior CABG for emergency surgery is listed year by year in Table I. The clinical characteristics of the patients are listed in chronological order of referral for emergency CABG in Table II. Their mean age was 61 years (range 50 to 78) and 16 were men. A single prior CABG had been performed in 16 patients, 2 prior CABGs in 2 patients and 3 prior CABGs in 1 patient. Two patients had preexisting left internal mammary artery grafts. The interval from the most recent CABG to the failed coronary angioplasty was 6.8 years (range 1 to 16). Angina symptoms were class II in 1 patient, class III in 5 patients and class IV in 13 patients. The number of diseased vessels present was 2 in 3 patients and 3 in 16 patients. A prior myocardial infarction had occurred in 11 patients. The mean left ventricular ejection fraction before coronary angioplasty was 54% (25 to 78%) and was $\leq 40\%$ in 4 patients. Before coronary angioplasty, 4 patients were judged to be very poor surgical candidates due to multiple prior CABGs (1 patient), only a single conduit supplying the myocardium (2 patients) and severely depressed ventricular function (1 patient).

TABLE I Referral for Emergent Bypass Surgery for Failed Elective Angioplasty in Patients with Prior Coronary Artery Bypass Grafting, 1980 to 1989

Year	Elective PTCA After CABG	Emergency CABG	Postoperative Death
1980	3	0	0
1981	19	1	0
1982	87	2	1
1983	177	3	0
1984	240	4	1
1985	325	2	0
1986	297	2	1
1987	331	2	0
1988	311	0	0
1989	346	3	0

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.

Angioplasty results: In 16 patients acute closure of a major vessel occurred in the catheterization laboratory associated with pain and electrocardiographic evidence of a current of injury. In 3 additional patients severe chest pain occurred either in the postprocedural observation area or on a ward. These patients were initially transferred to the catheterization laboratory for attempted stabilization of the dissected vessel but were then referred directly to the operating room. In 12 patients the acutely closed vessel was a native coronary artery that was never bypassed or had complete occlusion of the corresponding bypass graft, and in 7 patients it was a saphenous vein graft (6 body, 1 distal anastomosis). In 3 patients an intraaortic balloon pump was placed for severe hemodynamic instability (patients 3, 7 and 12) before transfer to the operating room. Two patients required cardiopulmonary resuscitation during transfer (patients 7 and 12). Anterograde coronary perfusion was maintained during transfer with continuous manual perfusion of blood through the balloon catheter in 1 patient and with an autoperfusion balloon catheter in an additional patient.

Surgical and hospital results: A total of 34 saphenous vein grafts and 1 internal mammary artery graft were placed emergently in the 19 patients. Three patients (patients 3, 7 and 12) could not be weaned from cardiopulmonary bypass and died in the operating room. All 3 patients were among those judged to be very poor surgical candidates due to multiple prior CABGs in 1 and only a single conduit to the heart in the 2 others. Three additional patients required an intraaortic balloon pump to assist in weaning from cardiopulmonary bypass and 3 required brief pressor support. Postoperative recoveries were generally uneventful in the 16 survivors with the exception of 1 patient (patient 14) who developed an acute respiratory distress syndrome, sepsis and disseminated intravascular coagulation postoperatively, eventually requiring bilateral amputations at the ankle. The average length of hospital stay was 16 days. Serial electrocardiograms demonstrated new Q waves indicating "definite" periproce-

TABLE II Characteristics of Patients Requiring Emergent Repeat CABG After Failed Elective Coronary Angioplasty

Pt.	Age (yrs) & Sex	Prior CABG (yrs)	Angina Class	Prior MI	Other Disease	LVEF (%)	Vessel Closure	Hospital Death	Length of Stay (days)	Q-Wave MI
1	78, M	3	IV	0	DM	60	LAD	0	18	+
2	61, F	2	III	+	0	61	LC	0	11	0
3	60, M	7	IV	+	0	60	LM LC	+	—	—
4	64, M	7	IV	0	0	56	SVG-LAD	0	10	0
5	56, M	5	III	0	SH	60	SVG-LAD	0	11	+
6	63, M	11	II	+	SH	40	LAD	0	12	0
7	57, F	6	IV	+	SH Leukemia	40	SVG-Right	+	—	—
8	59, M	1	IV	0	0	60	LAD	0	28	0
9	59, M	6	IV	0	SH	55	LAD	0	10	0
10	63, M	12	III	+	SH	32	Right	0	11	0
11	70, M	13	IV	+	SH	78	SVG-LAD	0	17	0
12	55, M	4, 15, 17	IV	+	DM, CVA	43	LM	+	—	—
13	65, M	10	IV	+	SH	76	SVG-Right	0	15	0
14	61, M	16	IV	0	SH	60	SVG-LAD	0	61	+
15	50, M	6, 15	III	+	0	60	SVG-Right	0	10	0
16	57, M	4, 6	II	0	0	60	LAD	0	13	+
17	75, F	3	IV	+	COPD	25	LC	0	20	0
18	59, M	8	IV	+	0	50	LC	0	8	0
19	54, M	5	IV	0	0	50	LAD	0	8	0

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; DM = diabetes mellitus; LAD = left anterior descending artery; LC = left circumflex; LM = left main; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SH = systemic hypertension; SVG = saphenous vein graft; + = present; 0 = absent.

dural myocardial infarctions in 4 patients. In an additional 4 patients elevations in creatine kinase levels were demonstrated without new Q waves, suggesting "probable" periprocedural infarctions. No patients were treated for congestive failure before discharge.

Late follow-up: The late outcome of all hospital survivors was available for analysis at a mean of 52 months (3 to 99 months). One patient (patient 12) died of an acute myocardial infarction 38 months after surgery. Of the 15 surviving patients, 10 reported no angina and 5 reported mild symptoms with ordinary activities. Six patients required coronary angioplasty to graft lesions from 4 to 88 months postoperatively. No subsequent CABGs were performed. No additional myocardial infarctions occurred.

DISCUSSION

The results of this study from a single experienced group of interventional cardiologists demonstrate that emergency repeat CABG after failed elective coronary angioplasty is very uncommon. Rates of emergency CABG were actually lower in prior CABG patients than in patients without prior CABG, indicating that they are not a high-risk group. The in-hospital survival rate was good, and all 3 patients who died in the operating room had high-risk characteristics that were identified before angioplasty. The other patients tolerated the ischemic insult relatively well. Evidence for periprocedural infarction was infrequent and did not result in congestive symptoms. Finally, long-term outcome was excellent, with most patients surviving with little or no angina.

Killen et al¹⁴ reported 286 patients requiring emergent or elective CABG after coronary angioplasty be-

tween 1980 and 1984, including 42 patients with prior CABG. These patients were referred from the 2 cardiology groups at our institution. In 115 patients, symptoms necessitated immediate transfer to surgery. Nine patients in the present report were included among those 115 patients. In the total group of 286 patients, 30-day mortality was 6.3%. Predictors of operative death in the combined group of elective and emergent procedures included emergency operation, prior CABG, multivessel coronary artery disease and preoperative cardiogenic shock.¹⁴

In this series, over half of the closures after coronary angioplasty occurred in native coronary arteries that were never bypassed or had occluded saphenous vein grafts. The 7 saphenous vein grafts that were involved closed due to intimal dissections, and graft embolization was not a factor. Prolonged inflations with autoperfusion catheters, and intravascular stents, laser balloon angioplasty and atherectomy all show promise for the emergent stabilization of significant intimal dissections.²⁴⁻²⁶ For patients in whom these new technologies fail or where they are not available, perfusion catheters permit stabilization of many patients en route to surgery.^{24,27,28} Although these devices were used infrequently in this series because they only became available recently, their use in patients with prior CABG will likely reduce the need for emergency surgery²⁶ and the incidence of Q-wave infarctions,²⁸ and permit greater use of the internal mammary artery.²⁷ Currently, our management of acute closure in patients with and without prior CABG includes prolonged inflations with standard or autoperfusion balloon catheters as attempts to tack down the intimal flap. If this fails, consideration is given to directional atherectomy.²⁶ This approach is

commonly limited by anatomic considerations prohibiting delivery of the bulky cutter in the current device. If emergency CABG is necessary, patients are transferred to the operating room with an autoperfusion catheter in place.

Patients with prior CABG have been considered potential candidates for routine supported angioplasty based on concerns about the possibility of acute closure and emergency surgery. The results of this study indicate that the routine use of supported coronary angioplasty is not necessary in patients with prior CABG. However, in selected patients with prior CABG and additional high-risk features such as severely depressed ventricular function or requiring dilatations of the only remaining circulation to the heart, use of support with an intraaortic balloon pump or cardiopulmonary bypass merits consideration.^{29,30}

The current study has several limitations. Although this report describes an unselected series of patients, it is retrospective and spans a period of major changes in coronary angioplasty technology and experience. The use of auxiliary devices, such as autoperfusion catheters, was not uniform. The indications for referral to emergency CABG were not established by protocol and biases in patient selection cannot be excluded. Finally, the small number of patients does not permit identification of clinical or angiographic factors predicting the need for emergency repeat CABG.

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Role of Tricuspid Regurgitation and Left Ventricular Damage in the Treatment of Right Ventricular Infarction-Induced Low Cardiac Output Syndrome

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To evaluate, in right ventricular (RV) myocardial infarction, the role of tricuspid regurgitation (TR) and left ventricular (LV) damage and the response to treatment of low cardiac output, 20 patients were prospectively studied. Volume infusion increased cardiac output only slightly (11%, $p < 0.001$), despite a dramatic increase in ventricular filling pressures. Dobutamine ($4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) markedly increased cardiac output (24%, $p < 0.001$) with a decrease in ventricular filling pressures. In the 5 patients with TR, dobutamine only modestly increased cardiac output (9 vs 26%, $p < 0.001$), while stroke index and LV end-diastolic dimensions decreased in comparison (-5 vs 33% and -6 vs 9%, respectively, $p < 0.001$). In the absence of TR ($n = 15$), there was no significant difference in response to volume expansion between patients with normal ($n = 7$) and depressed LV ejection fraction ($n = 8$). In contrast, dobutamine, in patients with depressed LV function, induced a greater increase in cardiac output (38 vs 17%, $p < 0.01$) and RV ejection fraction (36 vs 12%, $p < 0.05$). All patients with RV infarction-induced low cardiac output responded only modestly to volume loading. Dobutamine is particularly efficacious in patients without TR who have depressed LV function by improving RV function and, consequently, LV preload. In the 5 patients with TR, increasing RV contractility failed to improve the forward stroke volume by increasing the regurgitant fraction.

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Right ventricular (RV) myocardial infarction may complicate up to 25% of cases of acute inferior transmural left ventricular (LV) myocardial infarction. Significant hemodynamic alterations may be present in up to 10% of these patients.¹ Tricuspid regurgitation (TR) in this setting has not been well studied. Clinical recognition of TR is difficult in association with a low cardiac output, although it has been recently reported to occur in up to 35% of patients with RV infarction.² The magnitude of LV dysfunction contributes to the spectrum of hemodynamic changes.³ Regardless of LV damage, LV filling pressures remain low because of depressed RV output and thereby may go unrecognized. Direct evaluation is therefore necessary. In evaluating possible treatment strategies, consideration must be given to the degree of LV dysfunction. In this study, we examined the RV response to volume loading and gradual inotropic support in patients with low cardiac output and RV infarction, using a rapid computerized thermodilution method to assess RV performance at the bedside. Simultaneous radionuclide angiograms were used to stratify patients according to LV involvement.

METHODS

Patients: Over a 4-year period, 20 consecutive patients (13 men, 7 women, mean age of 59 years, range 38 to 75) with RV infarction and low cardiac output within 48 hours of the onset of symptoms were prospectively studied. Four patients had a history of nontransmural myocardial infarction and 8 had prior hypertension. Criteria for diagnosis of RV infarction were the following: symptoms consistent with prolonged ischemic chest pain; ST-segment elevation followed by the appearance of pathologic Q waves of ≥ 0.04 second in duration in leads II, III, aVF, V₃R and V₄R; elevation of total and MB creatine kinase serum levels; and scintigraphic evidence of both depressed RV ejection fraction (< 0.40) and regional wall motion abnormalities.⁴ Low cardiac output syndrome was associated with signs of peripheral hypoperfusion, mental status changes and urinary output < 25 ml/min.

Patients with mechanical complications (acute mitral regurgitation, ventricular septal defect, tamponade or cardiac rupture) and hemodynamically significant arrhythmia were excluded from the study. Patients with evidence of prior pulmonary, valvular, pericardial, con-

genital or myocardial disease were also excluded. Patients all received initially cautious volume expansion. Fifteen of the patients were studied before the thrombolytic era and the remaining 5 either had specific contraindications or were admitted belatedly. This study was approved by the ethics committee of our institution and informed consent was obtained from patients or families.

Hemodynamic and thermodilution measurements

A quadruple-lumen, pulmonary artery catheter (model 93A-431H-7.5F, American Edwards Laboratories) equipped with a fast-response thermistor (95 ms) was inserted. Cardiac output and RV ejection fraction were measured by a previously described⁵ and recently improved⁶ thermodilution technique (REF1 prototype 2, Edwards Laboratories) using an average of 3 serial determinations. Heart rate and systemic arterial pressure (cuff sphygmomanometer) were recorded.

Radionuclide measurements: DATA ACQUISITION

Thirty minutes before beginning the scintigraphic study, 15 mg of stannous pyrophosphate was given intravenously. Multigated blood-pool imaging was done 10 minutes after injection of technetium-99 in the antecubital vein. Patients were studied supine with the detector oriented in a 30 to 50° left anterior oblique incidence with 5 to 10° of craniocaudal tilt. Sixteen frames per cardiac cycle were acquired in a cine mode using a gamma camera (Acticamera CGR) equipped with high resolution (6 mm) low energy parallel holes collimator and a nuclear medicine computer (Imac CGR). Individual frames contained >250,000 counts and were recorded in a 64 × 64 matrix.

Data analysis: The data were analyzed by a technician who was blinded to the hemodynamic results, using a previously described semiautomatic program.⁷ Laboratory normal value for LV ejection fraction is 0.65 ± 0.06 .

Echocardiographic methods: M-mode and 2-dimensional echocardiograms were recorded with a Hewlett-Packard phased-array ultrasonograph. The apical 4-chamber incidence was used to obtain a qualitative estimation of the RV cavity size. End-diastolic diameters were measured by M-mode echocardiograms in the parasternal incidence. Because paradoxical septal motion in RV infarction is frequently encountered,^{8,9} the systolic dimensions were not measured. An RV end-diastolic dimension $>14 \text{ mm} \cdot \text{m}^{-2}$ or a ratio between RV/LV end-diastolic dimensions >0.70 were considered indicative of an enlargement of the right ventricle.^{10,11}

Patients were considered to have a hemodynamically significant TR by contrast echocardiography if all the following criteria were met: microcavitations passed back and forth across the tricuspid valve during successive cardiac cycle¹²; microcavitations appeared in both inferior vena cava and hepatic vein after atrial contraction and continued throughout systole and early diastole¹³; and microcavitations remained in the inferior vena cava for >10 systoles.

Patients with tricuspid regurgitation: Because thermal⁶ and nuclear¹⁴ determinations of RV ejection fraction and volumes are not a reliable measurement in pa-

tients with TR, assessment of changes in RV size of patients with TR may only be obtained by echocardiographic measure of end-diastolic RV dimensions.

Protocol: The protocol consisted of an initial simultaneous acquisition of echocardiographic, nuclear, hemodynamic and thermal measurements at baseline. At this point, radionuclide angiograms were used to stratify patients according to LV involvement. Echocardiography was used to assess RV and LV dimensions and contrast echocardiography to diagnose TR before insertion of the pulmonary artery catheter. During volume expansion and incremental increases in dobutamine levels, only the hemodynamic, thermal and echocardiographic measurements were performed at the bedside. Repeat nuclear determinations of RV ejection fraction in patients with TR were carried out. No patient had pulmonary artery wedge pressure $>18 \text{ mm Hg}$ and all received normal saline in 200 ml increments over 5 minutes. The volume administered was considered maximal when the pulmonary artery wedge pressure or right atrial pressures reached 20 mm Hg. Dobutamine was then infused in all patients at an initial rate of $4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and increased to $8 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

Statistical analysis: All data are presented as mean \pm standard deviation in the text and in the Tables. Mean \pm standard error of the mean is shown in Figure 1. In all patients, 1-way analyses of variance for repeated measures were performed to determine whether significant differences existed between the hemodynamic values during the control period, volume loading and the 2 infusion rates of dobutamine. When a difference was found, multiple Student *t* tests were performed to identify intergroup differences. Bonferroni correction was used to ensure a 0.05 *p* value. Analyses of variance for repeated values were also performed to determine the role of TR and LV damage on hemodynamics for the

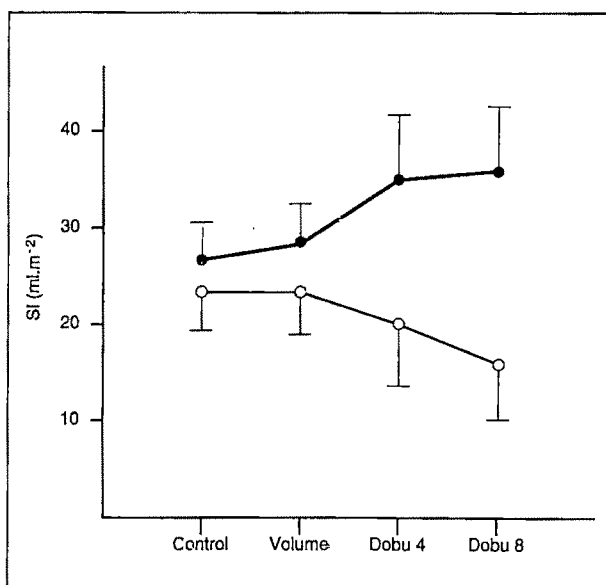


FIGURE 1. Variations of stroke index (SI) in response to therapy in the group with (open circle) and without (solid circle) regurgitation. Intergroup differences and variations are all statistically significant ($p < 0.001$).

TABLE I Effects of Volume Loading and Dobutamine in All Patients (n = 20)

	HR (beats · min ⁻¹)	CI (liters · min ⁻¹ · m ⁻²)	SI (ml · m ⁻²)	Mean BP (mm Hg)	PAP (mm Hg)	PWP (mm Hg)	RAP	RA:WP
Control	78 ± 12	1.9 ± 0.3	25 ± 4	75 ± 8	18 ± 2	12 ± 4	10 ± 3	0.95 ± 0.55
Volume	76 ± 10	2.1 ± 0.4	27 ± 5	78 ± 7	24 ± 2	18 ± 3	18 ± 3	1.04 ± 0.26
Dobu 4	84 ± 11	2.6 ± 0.6	31 ± 9	82 ± 9	22 ± 2	15 ± 2	15 ± 3	0.99 ± 0.26
Dobu 8	92 ± 15	2.7 ± 0.7	30 ± 11	84 ± 11	21 ± 3	14 ± 2	14 ± 4	1.06 ± 0.34
STAT	A*B†C‡	A†B†C‡	A†B†	A†B†C‡	A†B†C*	A†B†C†	A†B†	
	SVR (dynes s cm ⁻⁵)	TPR (dynes s cm ⁻⁵)	PVR (dynes s cm ⁻⁵)	RVSWI (g · m ⁻²)	LVSWI (g · m ⁻²)	RVEDD	LVEDD	RV:LVD
Control	1567 ± 272	489 ± 146	164 ± 99	2.9 ± 1.2	21 ± 5	18 ± 3	20 ± 6	0.96 ± 0.27
Volume	1374 ± 227	556 ± 142	143 ± 110	2.1 ± 1.1	22 ± 5	21 ± 3	22 ± 5	1.01 ± 0.27
Dobu 4	1282 ± 272	420 ± 160	126 ± 96	2.9 ± 1.8	28 ± 9	20 ± 3	23 ± 6	0.91 ± 0.30
Dobu 8	1273 ± 275	401 ± 195	144 ± 117	2.8 ± 1.8	30 ± 12	18 ± 3	23 ± 8	0.84 ± 0.30
STAT	A†B†	B†		A*B*	B†	A†B†C†	A*	A†B†C†

* p < 0.01; † p < 0.001; ‡ p < 0.05.
 BP = arterial pressure; CI = cardiac index; Dobu 4 = dobutamine at an infusion rate of 4 μg · kg⁻¹ · min⁻¹; Dobu 8 = dobutamine at an infusion rate of 8 μg · kg⁻¹ · min⁻¹; HR = heart rate; LVEDD = echocardiographic left ventricular end-diastolic dimension; LVSWI = left ventricular stroke work index (g · m⁻²); PAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; PWP = mean pulmonary wedge pressure; RAP = mean right atrial pressure; RA:WP = ratio between right atrial and pulmonary wedge pressures; RVEDD = echocardiographic right ventricular end-diastolic dimension; RV:LVD = right ventricular to left ventricular end-diastolic dimension ratio; RVSWI = right ventricular stroke work index; SI = stroke index; SVR = systemic vascular resistance; TPR = total pulmonary resistance; Volume = volume expansion.
 Statistical analysis (STAT): A = significant difference between control and volume; B = significant difference between volume and Dobu; C = significant dose effect of Dobu.

different therapeutic interventions. A p value ≤ 0.05 was considered to be statistically significant.

RESULTS

Initial left and right ventricular performances: Upon initial evaluation, the mean right atrial and pulmonary wedge pressures were high, and the ratio of these 2 pressures was ≥ 0.8 in 9 patients (45%) (Table I). Fourteen patients (70%) had either a right atrial pressure ≥ 10 mm Hg, or a right atrial:pulmonary wedge pressure ratio ≥ 0.8. Cardiac index was < 2.5 liters · min⁻¹ · m⁻² in all patients. The initial LV ejection fraction averaged 0.49 ± 0.13 and was depressed in 9 patients (0.29 to 0.42) and subnormal or normal in 11 (≥ 0.50). The end-diastolic volume and dimension were low and were linearly correlated with the stroke index ($y = 0.13x + 17.58$, $r = 0.60$, $p < 0.01$; and $y = 0.38x + 17.29$, $r = 0.52$, $p < 0.03$, respectively). In contrast, there was no correlation between LV end-diastolic volume (or dimension) and pulmonary wedge pressure.

RV ejection fractions were depressed (≤ 0.35) in all patients. RV end-diastolic volumes and echocardiographic dimensions were moderately increased. The ratio between RV and LV end-diastolic volumes and dimensions were elevated. The correlation between RV end-diastolic volume and echocardiographic dimension in patients without TR was good ($y = 5.57x + 7.38$, $r = 0.86$, $p < 0.001$, $n = 15$). In contrast to the left ventricle, no correlation was found between RV end-diastolic volume (or dimension) and stroke index. Contrast echocardiography showed a significant TR in 5 of the 20 patients, in whom only 3 had a prominent right atrial V pressure wave. In these 5 patients, the thermidilution curve was flat and prolonged and did not exhibit the series of descending plateaus. At baseline (Table II), these patients had higher right atrial pressure (+44%) and equalization of the ventricular filling pressures with preferential enlargement of the right ventricle. The cardiac index was also lower.

Therapeutic interventions: Volume infusion (average, 595 ± 240 ml) was followed by a dramatic increase in both RV and LV filling pressures, a small increase of the ventricular diameters and cardiac index unrelated to the initial RV filling pressure and RV end-diastolic diameter (Table I). In contrast, only a slight increase in arterial pressure and cardiac and stroke indexes was observed. In the 5 patients with TR, there was no change in cardiac index.

Dobutamine infusion (4 μg · kg⁻¹ · min⁻¹) decreased both RV and LV filling pressures (-20%) with only a slight decrease in RV end-diastolic dimension (-5%). Cardiac index markedly increased (+24%) by increases in both stroke index and heart rate. In the 15 patients without TR, RV ejection fraction improved (+16%) with no change in end-diastolic volume. Conversely, in the 5 patients with TR, dobutamine dramatically increased heart rate (+25%), but did not change stroke index.

With increasing dobutamine dosage (8 μg · kg⁻¹ · min⁻¹), cardiac index continued to increase, essentially through an increase in heart rate (+10%). In patients with TR, this dosage was followed by a further increase in heart rate (+24%) accompanied by a decrease in stroke volume and RV end-diastolic dimension, while right atrial pressure increased. One patient developed transient atrial fibrillation and 2 patients with TR developed chest pains with electrocardiographic modifications that disappeared with lowering of dosages.

Comparison between the effects of volume loading and dobutamine in patients with and without significant tricuspid regurgitation: In patients with TR (group I, n = 5) volume expansion was significantly less efficacious in increasing overall cardiac performance than those without TR (group II, n = 15) (Table II, Figure 1). During dobutamine infusion (4 μg · kg⁻¹ · min⁻¹), the modest increase in cardiac index in group I (9 vs 26%) was essentially due to an increase in heart rate, while stroke index and LV end-diastolic dimen-

TABLE II Comparison Between Patients With (n = 5) and Without (n = 15) Initial Tricuspid Regurgitation

TR	HR (beats · min)		CI (liters · min ⁻¹ · m ⁻²)		SI (ml · m ⁻²)		Mean BP (mm Hg)		PAP (mm Hg)	
	+	0	+	0	+	0	+	0	+	0
Control	69 ± 7	81 ± 12	1.6 ± 0.2	2.0 ± 0.2	23 ± 4	26 ± 4	70 ± 5	76 ± 8	19 ± 2	18 ± 3
Volume	69 ± 7	78 ± 10	1.6 ± 0.2	2.2 ± 0.2	23 ± 4	28 ± 4	72 ± 5	80 ± 7	24 ± 1	24 ± 3
Dobu 4	86 ± 10	83 ± 10	1.7 ± 0.3	2.8 ± 0.3	20 ± 6	34 ± 7	74 ± 6	85 ± 5	22 ± 1	21 ± 3
Dobu 8	106 ± 14	88 ± 13	1.6 ± 0.3	3.0 ± 0.3	16 ± 6	35 ± 7	72 ± 6	88 ± 9	22 ± 2	20 ± 3
STAT	D*G†Y‡		D†E*F*G*X*Y‡Z*		E‡F*G*X*Y*Z‡		E*F*G†		Y‡Z†	
TR	PWP (mm Hg)		RAP		RA:WP		SVR (dynes · cm ⁻⁵)			
	+	0	+	0	+	0	+	0		
Control	11 ± 4	12 ± 4	13 ± 2	9 ± 3	1.48 ± 0.86	0.77 ± 0.25	1686 ± 309	1527 ± 258		
Volume	16 ± 3	19 ± 3	19 ± 2	13 ± 3	1.27 ± 0.27	0.97 ± 0.22	1538 ± 255	1320 ± 196		
Dobu 4	15 ± 2	16 ± 1	17 ± 2	14 ± 3	1.22 ± 0.28	0.91 ± 0.21	1568 ± 324	1186 ± 177		
Dobu 8	13 ± 2	14 ± 2	19 ± 2	13 ± 3	1.46 ± 0.24	0.92 ± 0.24	1530 ± 347	1187 ± 192		
STAT			D*G*X*Y*Z†		D*E*F*G*X*Y*Z*		F*G*			
TR	TPR (dynes · cm ⁻⁵)		PVF (dynes · cm ⁻⁵)		RVSW (g · m ⁻²)		LVSW (g · m ⁻²)			
	+	0	+	0	+	0	+	0		
Control	566 ± 95	464 ± 153	248 ± 148	136 ± 61	1.8 ± 1.5	3.2 ± 0.8	18 ± 3	22 ± 5		
Volume	735 ± 163	497 ± 68	271 ± 142	109 ± 53	1.5 ± 0.4	2.3 ± 1.3	17 ± 3	24 ± 5		
Dobu 4	628 ± 194	350 ± 58	234 ± 130	90 ± 46	1.4 ± 0.7	3.4 ± 1.8	16 ± 4	32 ± 7		
Dobu 8	667 ± 237	312 ± 45	266 ± 181	103 ± 46	0.9 ± 1	3.4 ± 1.5	13 ± 5	35 ± 8		
STAT	E‡F*G*Y*Z*		D†E*F*G*X†		D†F*G*Y*		E*F*G*X†Y†Z†			
TR	RVEF		RVEDD		LVEDD		RV:LVD			
	+(N)	0(TD)	+	0	+	0	+	0		
Control	0.26 ± 0.04	0.25 ± 0.05	20 ± 3	17 ± 3	17 ± 4	21 ± 6	1.24 ± 0.32	0.87 ± 0.18		
Volume	0.25 ± 0.03	0.29 ± 0.06	23 ± 2	20 ± 4	18 ± 4	23 ± 5	1.28 ± 0.32	0.92 ± 0.18		
Dobu 4	0.29 ± 0.04	0.29 ± 0.07	21 ± 2	19 ± 3	17 ± 4	25 ± 5	1.30 ± 0.34	0.78 ± 0.13		
Dobu 8	0.29 ± 0.04	0.31 ± 0.07	18 ± 2	13 ± 3	15 ± 4	25 ± 5	1.25 ± 0.32	0.70 ± 0.11		
STAT					F†G†Y†		D*E*F*G*Y*			

*p < 0.01; †p < 0.05; ‡p < 0.001.

N = nuclear; RVEF = right ventricular ejection fraction; TD = thermal; TR = tricuspid regurgitation. Other abbreviations as in Table I.

Statistical analysis (STAT): D = significant difference between TR⁺ control and TR⁰ control values; E = significant difference between TR⁺ volume and TR⁰ volume values; F = significant difference between TR⁺ Dobu 4 and TR⁰ Dobu 4 values; G = significant difference between TR⁺ Dobu 8 and TR⁰ Dobu 8 values; X = significant difference of variation induced by volume between TR⁺ and TR⁰ values; Y = significant difference of variation induced by Dobu between TR⁺ and TR⁰ values; Z = significant difference in dose effect of Dobu between TR⁺ and TR⁰ values.

sions tended to decrease in contrast to group I (−5 vs 33% and −6 vs 9%, respectively). Higher levels of dobutamine were followed by a greater increase of heart rate in group I (23 vs 6%) associated, in contrast to group II, with a decrease in cardiac and stroke indexes (−6 vs 7% and −20 vs 9%, respectively). The right atrial pressure rose in group I while this pressure continued to decrease in group II (−19 vs 9%). The observed increase in pressure was associated with a decrease in RV end-diastolic dimension (−26%) in group I.

In the absence of TR, comparison between the effects of volume loading and dobutamine in patients with normal and depressed LV ejection fraction: No significant difference was observed between the two groups with volume expansion (Table III). Conversely, with dobutamine infusion (4 μg·kg^{−1}·min^{−1}), patients with depressed LV function (group IIb, n = 3) had a greater increase in cardiac and stroke indexes than patients with conserved LV function (group IIa, n = 7) (38 vs 17% and 25 vs 14%, respectively), associated with a smaller increase in heart rate. Total pulmonary vascular resistance decreased more in group IIb (43 vs 19%),

associated with a greater increase in RV ejection fraction (36 vs 12%).

In-hospital mortality: Three patients (15%) died during the hospital course: 2 secondary to a large biventricular myocardial infarction (1 despite severe clinical regurgitation; no anomaly of the tricuspid valve was evidenced) and the third of extensive grade IV¹ RV infarction (without severe LV damage), associated with a tricuspid papillary muscle rupture.

DISCUSSION

The major findings of this study in patients with RV infarction-induced low cardiac output are the following: volume loading was only modestly effective in restoring cardiac output; dobutamine produced substantial improvement of cardiac performance; severe TR rendered all treatment ineffective; and altered hemodynamic status with concomitant LV damage was amenable to treatment with dobutamine.

Limitations of methodology: Precise analysis of RV response to treatment requires accurate determination of ventricular volumes. The choice of nongeometric

TABLE III In the Absence of Tricuspid Regurgitation (n = 15), Comparison Between Patients with Normal (n = 7) and Depressed Initial Left Ventricular Ejection Fraction (n = 8)

	HR (beats · min ⁻¹)		CI (liters · min ⁻¹ · m ⁻²)		SI (ml · min ⁻¹)		Mean BP (mm Hg)		PAP (mm Hg)	
LVEF	<0.45	>0.45	<0.45	>0.45	<0.45	>0.45	<0.45	>0.45	<0.45	>0.45
Control	79 ± 12	83 ± 12	2.1 ± 0.3	2.0 ± 0.2	26 ± 5	25 ± 3	77 ± 8	76 ± 8	18 ± 2	17 ± 3
Volume	76 ± 11	81 ± 10	2.1 ± 0.2	2.3 ± 0.2	28 ± 5	28 ± 3	80 ± 6	80 ± 8	24 ± 3	23 ± 3
Dobu 4	79 ± 10	87 ± 10	2.9 ± 0.4	2.7 ± 0.3	36 ± 8	32 ± 4	84 ± 7	85 ± 9	21 ± 3	22 ± 2
Dobu 8	82 ± 9	95 ± 13	3.1 ± 0.4	3.0 ± 0.3	38 ± 8	32 ± 5	87 ± 8	89 ± 10	20 ± 3	21 ± 3
STAT	Y*Z*		Y*		Y†Z†					
	PWP (mm Hg)		RAP		RA:WP		SVR (dynes s cm ⁻⁵)			
LVEF	<0.45	>0.45	<0.45	>0.45	<0.45	>0.45	<0.45	>0.45	<0.45	>0.45
Control	14 ± 3	10 ± 4	8 ± 2	9 ± 4	0.62 ± 0.17	0.95 ± 0.22	1555 ± 245	1496 ± 287		
Volume	21 ± 2	16 ± 2	17 ± 2	19 ± 4	0.82 ± 0.14	1.14 ± .15	1391 ± 133	1238 ± 233		
Dobu 4	16 ± 1	15 ± 1	13 ± 3	15 ± 3	0.84 ± 0.24	1.0 ± .15	1192 ± 174	1179 ± 195		
Dobu 8	14 ± 2	14 ± 2	12 ± 2	14 ± 4	0.86 ± 0.27	1.0 ± .20	1200 ± 215	1171 ± 177		
STAT	E*Y†				D*E†Y†					
	TPR (dynes s cm ⁻⁵)		PVR (dynes s cm ⁻⁵)		RVSWI		LVSWI			
LVEF	<0.45	>0.45	<0.45	>0.45	<0.45	>0.45	<0.45	>0.45	<0.45	>0.45
Control	433 ± 52	500 ± 221	107 ± 63	169 ± 39	3.5 ± 0.7	2.9 ± 0.9	21 ± 4	23 ± 7		
Volume	527 ± 74	463 ± 43	93 ± 63	127 ± 36	2.8 ± 0.9	1.7 ± 1.3	23 ± 4	25 ± 5		
Dobu 4	336 ± 70	336 ± 38	82 ± 57	100 ± 33	3.8 ± 2.0	3.0 ± 1.4	33 ± 6	31 ± 8		
Dobu 8	300 ± 50	327 ± 36	98 ± 60	109 ± 28	4.2 ± 2.0	3.2 ± 1.5	38 ± 7	33 ± 9		
STAT	Y†									
	LVEDD		RVEF		RVEDV (ml · m ⁻²)		RVESV (ml · m ⁻²)			
LVEF	<0.45	>0.45	<0.45	>0.45	<0.45	>0.45	<0.45	>0.45	<0.45	>0.45
Control	25 ± 6.0	17 ± 1.8	0.25 ± 0.07	0.25 ± 0.07	105 ± 20	104 ± 17	79 ± 20	79 ± 17		
Volume	26 ± 5.4	19 ± 1.5	0.25 ± 0.07	0.25 ± 0.04	127 ± 36	117 ± 15	97 ± 35	88 ± 15		
Dobu 4	28 ± 5.5	21 ± 0.8	0.31 ± 0.08	0.27 ± 0.06	119 ± 16	119 ± 13	83 ± 18	87 ± 16		
Dobu 8	30 ± 6.0	22 ± 1.5	0.34 ± 0.07	0.29 ± 0.07	115 ± 13	112 ± 14	77 ± 14	81 ± 17		
STAT	D*E†F*G*		Y†							

* p < 0.01; † p < 0.001; ‡ p < 0.05.
LVEF = left ventricular ejection fraction; RVEDVI = right ventricular end-diastolic volume index; RVEF = thermal right ventricular ejection fraction; RVESVI = right ventricular end-systolic volume index. Other abbreviations as in Table I.
Statistical analysis (STAT): D = significant difference between LVEF <0.45 control and LVEF >0.45 control values; E = significant difference between LVEF <0.45 volume and LVEF >0.45 volume values; F = significant difference between LVEF <0.45 Dobu 4 and LVEF >0.45 Dobu 4 values; G = significant difference between LVEF <0.45 Dobu 8 and LVEF >0.45 Dobu 8 values; X = significant difference of variation induced by volume between LVEF <0.45 and LVEF >0.45 values; Y = significant difference of variation induced by Dobu between LVEF <0.45 and LVEF >0.45 values; Z = significant difference in dose effect of Dobu between LVEF <0.45 and LVEF >0.45 values.

* p < 0.01; † p < 0.001; ‡ p < 0.05.

LVEF = left ventricular ejection fraction; RVEDVI = right ventricular end-diastolic volume index; RVEF = thermal right ventricular ejection fraction; RVESVI = right ventricular end-systolic volume index. Other abbreviations as in Table I.

Statistical analysis (STAT): D = significant difference between LVEF < 0.45 control and LVEF > 0.45 control values; E = significant difference between LVEF < 0.45 volume and LVEF > 0.45 volume values; F = significant difference between LVEF < 0.45 Dobu 4 and LVEF > 0.45 Dobu 4 values; G = significant difference between LVEF < 0.45 Dobu 8 and LVEF > 0.45 Dobu 8 values; X = significant difference of variation induced by volume between LVEF < 0.45 and LVEF > 0.45 values; Y = significant difference of variation induced by Dobu between LVEF < 0.45 and LVEF > 0.45 values; Z = significant difference in dose effect of Dobu between LVEF < 0.45 and LVEF > 0.45 values.

methods for measuring RV ejection fraction and volumes seems most appropriate, given the variable shape of the right ventricle. If cardiac output determination by thermodilution and, therefore, forward stroke volume has usually been considered reliable^{15,16} in the presence of TR, the thermal⁶ and nuclear¹⁴ determination of RV ejection fraction is not accurate in this clinical setting. The RV ejection fraction measured by radionuclide technique is actually the global ejection fraction (EF), defined as the forward (f) plus the regurgitant (r) stroke volume (SV) divided by the end-diastolic volume (EDV): global EF = [SVf + SVr]/EDV. The RV end-diastolic volume cannot be calculated from nuclear RV ejection fraction (global EF) and thermal stroke volume (SVf), because the regurgitant stroke volume remains unknown. Assessment of changes in RV size of patients with TR can only be obtained by echocardiographic measure of RV end-diastolic dimensions.

Volume loading: Volume loading was the first and extensively documented therapeutic intervention,^{10,17-22} but its mechanism has not been clearly elucidated and

its clinical efficacy not firmly established. Volume loading in hemodynamically significant RV infarction was reported by Cohn et al¹⁷ to be quite efficacious. Further reports tempered these findings; slightly increased cardiac output (≤10%), as in our 20 patients and others, was observed⁴ or there was no increase at all.¹⁹⁻²⁰ One of the groups²⁰ has argued that the beneficial effect of volume loading observed⁴ might be explained by an initial cardiac output ≥2.6 liters·min⁻¹·m⁻². This fails to explain the improvement observed in our study. Another possibility could be differences in the initial fluid status. Initial RV filling pressures and end-diastolic dimensions were not correlated with the response to volume loading.

Several mechanisms may limit the efficacy of volume loading. After volume infusion, we observed the following: a dramatic increase of right atrial pressures and pulmonary wedge pressure with consequent pressure equalization; a modest rise of RV and LV end-diastolic dimensions; a parallel augmentation of stroke volume with the increased end-diastolic dimensions of

the left ventricle but not with that of the right ventricle; and an increase of the RV:LV end-diastolic ratio. The subsequent disproportionate increase of intracavitary pressures with respect to diastolic dimensions suggests that transmural pressures are of a smaller magnitude consequent to an increased intrapericardial pressure, as has been observed by Goldstein et al¹⁸ in the dog. An altered diastolic compliance of the right ventricle may also play a role. Furthermore, ventricular interference is suggested by a continued increase of the RV:LV diastolic dimension ratio to values >1 . We conclude that further increase of RV volumes to bring the Starling's law into play is limited by the increased intrapericardial pressures and ventricular interference.

Dobutamine infusion ($4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) in the 15 patients without TR led to a marked improvement of RV contractility, as judged by increased stroke volume, stroke work and ejection fraction associated with decreased filling pressures and dimensions. The improvement of RV performance was followed by a decrease in LV filling pressures with no change in diastolic dimensions, suggesting a decreased ventricular interference, decreased intrapericardial pressure or both. Increasing the dosage of dobutamine was only accompanied by a progressive decrease in filling pressures and an increase in heart rate and an additional volume expansion could have been beneficial. Similar results were obtained by Dell'Italia et al²⁰ using maximal doses that ranged from 5 to 20 (mean 13) $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. However they found no variations of LV filling pressure with dobutamine, probably because most of their patients had normal LV ejection fraction (0.60 ± 0.12 vs 0.49 ± 0.13 in our study). In the subgroup of our 7 patients with normal LV ejection fraction, there also was no decrease in the wedge pressure with dobutamine. In cases of normal LV function and RV infarction, pulmonary wedge pressure is essentially dictated by RV outflow and ventricular interference. In these patients, dobutamine increased RV outflow and decreased ventricular interference, thereby producing a balanced effect on the wedge pressure. In cases of severely depressed LV ejection fraction, LV function becomes the major determinant of the pulmonary wedge, and dobutamine may diminish the wedge pressure by increasing LV contractility. Similar results were observed with dopamine in a small group ($n = 4$) of such patients.¹⁹

Tricuspid regurgitation: TR in patients with RV infarction is a diagnostic and therapeutic challenge. No technique has been established as the gold standard in diagnosing TR. Only qualitative assessment is possible. Comparing echocardiographic method with RV contrast angiography, Curtius et al²³ concluded that both contrast and Doppler echocardiography were accurate methods for routine diagnosis of TR at bedside, with a sensitivity of 82 and 92%, respectively. Specificity was, however, superior with contrast echocardiography compared with Doppler technique (100 vs 86%). Only 5 patients with TR had a flat and prolonged thermodilution curve without descending plateaus, as recently reported.^{6,15} This is probably due to a to and fro movement of the cold bolus across the incompetent valve. The value

of this finding in the diagnosis of TR should be studied further.

The incidence of TR has been difficult to assess, because it has been primarily reported in the form of isolated cases²⁴ and recognition depends on the diagnostic procedure used.⁸ In our study, TR was judged to be present in 5 of the 20 patients (25%). Jugdutt et al,²⁵ using the same technique and criteria for the diagnosis of TR, found evidence of TR in 4 of their 17 patients (24%) in this clinical setting. In another, RV angiography was positive in 7 of their 20 patients (35%).² The slightly lower frequency of TR in our study may be partially explained by the fact that we have excluded a large group of patients with atrial arrhythmias, which are frequently associated with TR in RV infarction.²

The therapeutic response to fluid challenge and inotropic drugs in the presence of TR has not been reported. In the small number of patients with TR we studied, volume expansion failed to increase cardiac output. This is probably due to a more severe alteration in ventricular systolic and especially diastolic function in patients with TR (RV filling pressures were higher for similar end-diastolic dimensions, Table II). Most interestingly, dobutamine was unable to increase stroke volume despite an increased nuclear RV ejection fraction ($p < 0.06$) and constant end-diastolic dimensions. Nuclear RV ejection fraction represents the global ejection fraction; that is, forward stroke volume added to the regurgitant volume divided by the end-diastolic volume. If the end-diastolic dimension reflects the end-diastolic volume as accurately as in patients without TR, an increase of nuclear RV ejection fraction with no change in forward stroke volume and end-diastolic dimension implies an increase in the regurgitant volume. This was still more evident at $8 \mu\text{g}$ of dobutamine; a decrease in stroke volume and a marked increase in heart rate were noted. Concomitantly, right atrial pressure increased and end-diastolic dimension decreased, suggesting an additional decrease in RV compliance. This was probably due to tachycardia-induced imbalance between myocardial oxygen supply and demand, as shown in the 2 patients developing clinical and electrocardiographic signs of myocardial ischemia that were relieved after discontinuation of dobutamine.

Additional left ventricular damage: Surprisingly, volume loading was followed by a similar increase in RV and LV filling pressures, the right atrial:pulmonary wedge pressure ratio being, however, lower in patients with extensive LV damage. The increase in pulmonary wedge pressure did not correspond to an increased preload because LV end-diastolic dimensions remained constant. Elevated LV filling pressure in these patients is probably indicative of higher intrapericardial pressure secondary to RV dilatation, as in the dog model,²⁶ rather than consequent to the extensive LV damage. The dobutamine-induced increase of global and RV pump function was greater in patients with severe LV damage. The following 2 explanations may account for this: dobutamine-induced enhancement of LV ejection may thereby decrease the afterload of the right ventricle (greater decrease in total pulmonary resistance in this

group) and enhancement of LV ejection augments RV ejection (ventricular interdependence).

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The Divergent Recovery of ST-Segment Depression and Radionuclide Angiographic Indicators of Myocardial Ischemia

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This study evaluated the recovery after exercise of both ST-segment depression on the exercise electrocardiogram (electrical evidence of ischemia) and exercise-induced abnormalities in wall motion or ejection fraction as detected by radionuclide angiography. The study group of 31 patients was selected to undergo prolonged electrocardiographic and radionuclide imaging after exercise because they had persistent ST-segment depression >3 minutes after exercise and radionuclide angiographic evidence of ischemia at peak exercise. In 27 (87%) of the 31 patients, radionuclide evidence of ischemia recovered more quickly than the electrocardiogram. Only 15 of the 31 patients had exercise-induced radionuclide abnormalities after exercise. Compared with the 16 patients without such findings of ischemia after exercise, these 15 patients had a worse wall motion score at peak exercise (5.3 vs 3.5; $p < 0.01$) and a smaller increase in systolic blood pressure with exercise ($p < 0.05$) and after exercise ($p < 0.01$). Radionuclide angiographic evidence of ischemia recovers more quickly after exercise than ST-segment depression. When there is radionuclide evidence of ischemia after exercise, it is associated with more severe ischemia during exercise.

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The presence,¹ magnitude^{2,3} and configuration^{4,5} of ST-segment changes during exercise and the duration of ST-segment depression after exercise⁵⁻⁷ have been used to diagnose coronary artery disease and to predict outcome.⁸⁻¹² Exercise radionuclide angiography also has been used to diagnose coronary artery disease, assess disease severity,¹³⁻¹⁵ predict outcome^{16,17} and assess therapeutic interventions.¹⁸⁻²⁰ Upton et al²¹ found that exercise-induced left ventricular dysfunction may be detected before electrocardiographic ST-segment depression appears. However, the relation between the *postexercise* recovery of ST-segment depression on the exercise electrocardiogram and of exercise-induced abnormalities in wall motion and ejection fraction has not been previously examined. The purpose of this study was therefore to evaluate the time course of recovery of radionuclide angiographic evidence of ischemia after exercise in patients with persistent ST-segment depression after exercise.

METHODS

Study group: Patients undergoing clinically indicated supine exercise radionuclide angiography for the evaluation of chest pain were eligible for the study. Patients with resting ST-segment abnormality, left ventricular hypertrophy, left bundle branch block, Wolff-Parkinson-White syndrome, paced rhythm, hypothyroidism, hyperthyroidism or electrolyte disorders or those receiving digoxin therapy or psychotropic drug therapy were excluded.

The study group consisted of consecutive patients who were selected to undergo prolonged radionuclide imaging after exercise because they had ≥ 1 mm of horizontal or downsloping ST-segment depression 80 ms after the J point that persisted for 3 minutes after exercise and had a regional wall motion abnormality or a decrease in ejection fraction during exercise.

Exercise protocol: Patients underwent supine exercise bicycle ergometry according to a previously described protocol²² to 1 of the following endpoints: (1) severe angina pectoris, (2) marked fatigue, (3) complex ventricular ectopy or (4) 2 mm of horizontal or downsloping ST-segment depression. The exercise protocol was occasionally modified by the monitoring physician.

Although we recommended that antianginal medications be withdrawn before testing, 13 patients were taking β -adrenergic blockers at the time of testing.

Radionuclide methods: Our techniques for red blood cell labeling and equilibrium radionuclide angiography have been described previously.²²

Two-minute multigated radionuclide images were obtained at rest, for the last 2 minutes of each 3-minute exercise period and for 2 minutes after exercise ending at 3, 6, 9 and 12 minutes after exercise. For patient comfort, only the first postexercise acquisition was performed with the patient's feet up in the bicycle pedals. The patient was supine with both feet out of the bicycle pedals for the remaining 3 images. A 12-lead electrocardiogram was recorded at rest, every minute during exercise, at peak exercise, immediately after exercise and at 3, 6, 9 and 12 minutes after exercise. Electrocardiography was therefore performed at the end of each postexercise radionuclide acquisition. The blood pressure was recorded at rest and during each exercise radionuclide acquisition. The blood pressure was also recorded at 2 minutes after exercise in the last 15 patients.

A standard operator-assisted computer algorithm²² was used to calculate ejection fraction. Any decrease in ejection fraction was considered significant if the resting ejection fraction was <70%; if the resting ejection fraction was >70%, a decrease of at least 5% was required. Septal, inferoapical and posterolateral regional wall motions were evaluated by the consensus of 2 blinded observers on a 6-point scale (from 1, for normal, to 6, for dyskinetic). A regional wall motion abnormality was considered to be present if the score in any 1 of the 3 segments worsened from rest to peak exercise. The data were analyzed with the Student *t* test.

RESULTS

The time for postexercise recovery of ST-segment depression was clearly different from the time for recovery of radionuclide indicators of ischemia (Figure 1). By design, all 31 patients had both ST-segment depression and radionuclide evidence of ischemia at peak exercise and ST-segment depression that persisted for at least 3 minutes after exercise. However, only 15 had a decrease in ejection fraction or a regional wall motion abnormality that persisted after exercise. Of these 15 patients, in 11 the ST-segment depression persisted longer after exercise than the presence of radionuclide evidence of ischemia, in 2 the radionuclide ischemia persisted longer and in 2 both resolved simultaneously. Thus, in 27 (87%) of the 31 patients, radionuclide ischemia recovered more quickly than the electrocardiogram.

There were clear differences in the time course of recovery of both exercise-induced regional wall motion abnormalities and exercise-induced decrease in ejection fraction compared with ST-segment depression (Figure 2). At 3 minutes after exercise, only 14 patients (45%) had a persistent exercise-induced regional wall motion abnormality, although ST-segment depression was present in all 31 patients. The results were similar when decreases in ejection fraction were evaluated. At 3 minutes after exercise, a decrease in ejection fraction from the resting value was still present in 9 (29%) patients, although ST-segment depression was present in all 31 patients.

No significant differences were noted when patients with radionuclide evidence of ischemia and those with-

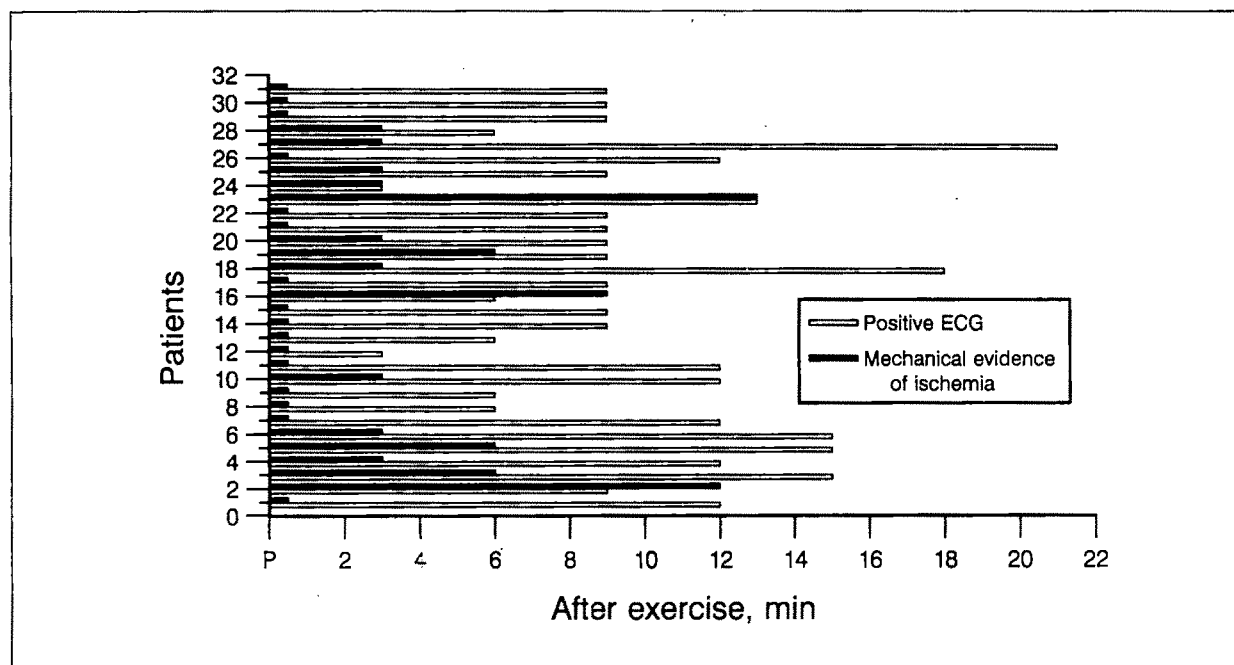


FIGURE 1. Electrocardiographic and mechanical radionuclide findings at peak exercise and after exercise for 31 patients. *Open bars* = duration of ST-segment depression after exercise; *solid bars* = duration of mechanical evidence of ischemia (either a wall motion abnormality or a decrease in ejection fraction) after exercise. Mechanical evidence of ischemia clearly resolves more quickly than ST-segment depression. ECG = electrocardiogram.

out were compared with respect to exercise METs, exercise rate-pressure product, peak exercise ST-segment depression, resting ejection fraction, exercise ejection fraction, change in ejection fraction with exercise and regional wall motion abnormalities at rest and with exercise (Table I).

The severity of ischemia at peak exercise influenced its postexercise recovery (Figure 3). The 15 patients with radionuclide evidence of ischemia after exercise had a worse mean wall motion score at peak exercise than the 16 patients without evidence of ischemia after exercise (5.3 vs 3.9 ; $p < 0.01$). Similar but insignificant trends were present for the ejection fraction data.

The 15 patients with radionuclide evidence of ischemia after exercise had ST-segment depression that tended to persist longer after exercise (11.4 ± 4.7 minutes) than in patients without radionuclide evidence of ischemia (8.8 ± 2.5 minutes), but this difference was of borderline significance ($p = 0.06$). The presence of radionuclide evidence of ischemia after exercise was associated with a lower systolic blood pressure during and after exercise. Postexercise blood pressure measurements were available for 15 patients (8 with radionuclide evidence of ischemia after exercise and 7 without) (Figure 4). The 7 patients without evidence of ischemia

after exercise had a greater increase in systolic blood pressure with exercise ($p < 0.05$) that persisted after exercise ($p < 0.01$) than the 8 patients with evidence of ischemia after exercise.

The persistence of ST-segment depression after exercise in the 13 patients who were receiving β -adrenergic blockers at the time of exercise testing (10 ± 3 minutes) was not significantly different from that in the 18 patients who were not receiving β -adrenergic blockers (10 ± 3 minutes). Of the 15 patients who had radionuclide evidence of ischemia after exercise, 7 were receiving β -adrenergic blockers; 6 of these 7 had persistence of ST-segment depression after resolution of radionuclide evidence of ischemia.

DISCUSSION

During the immediate postexercise period, there are relatively rapid reductions in venous return, stroke volume, heart rate and blood pressure that dramatically reduce cardiac workload and help to reverse cardiac ischemia if it is present.

The purpose of this study was to evaluate the time course of recovery of ST-segment depression and radionuclide indicators of ischemia. In 27 (87%) of 31 patients with persistent ST-segment depression after exer-

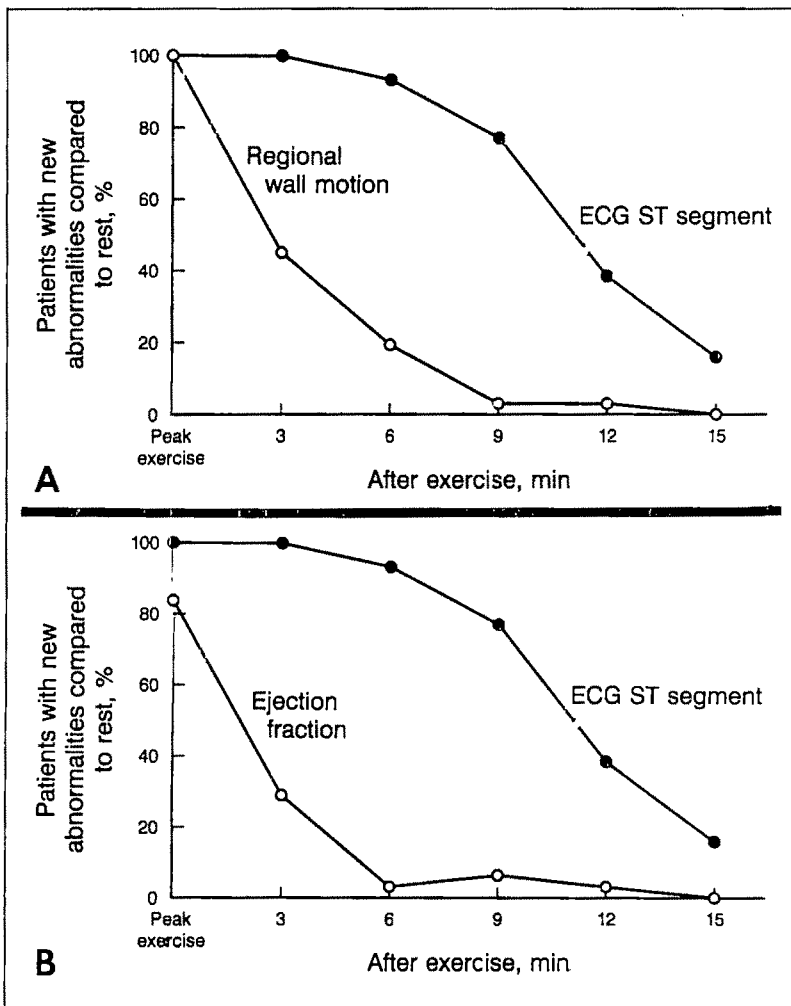


FIGURE 2. Percentage of patients with ST-segment depression and exercise-induced regional wall motion abnormalities (A) and exercise-induced decrease in ejection fraction (B) at peak exercise and after exercise. In both comparisons, radionuclide evidence of ischemia recovered considerably sooner than ST-segment depression ($p \leq 0.01$). ECG = electrocardiographic.

TABLE I Comparison of Patients with Radionuclide Angiography (RNA) Evidence of Ischemia After Exercise and Patients with Normal RNA Results After Exercise

	Patient Group		p Value
	Abnormal Postexercise RNA (n = 15)	Normal Postexercise RNA (n = 16)	
Exercise METs	4.87 ± 0.7	5.36 ± 1.4	NS
Exercise RPP	24,614 ± 6,675	20,577 ± 4,581	NS
Peak exercise ST-segment depression (mm)	2.7 ± 0.9	2.9 ± 1.4	NS
Duration of ST changes after exercise (minutes)	11.4 ± 4.7	8.8 ± 2.5	0.06
Resting EF (%)	57 ± 10	56 ± 9	NS
Exercise EF (%)	47 ± 10	51 ± 10	NS
Change in EF (%)	-9.8 ± 9.1	-5.0 ± 10.0	NS
Regional wall motion abnormalities at rest	2.2 ± 1.8	2.4 ± 1.3	NS
Regional wall motion abnormalities with exercise	5.3 ± 2.7	3.9 ± 1.9	NS
Change in regional wall motion abnormalities with exercise	3.1 ± 1.8	1.5 ± 1.7	<0.02
Change in BP (rest to peak exercise)*	16 ± 16	40 ± 22	<0.05
Change in BP (rest to after exercise)*	4 ± 7	16 ± 21	<0.01
Percentage taking β -adrenergic blockers	47%	40%	NS

* These data were available for 15 patients (8 with radionuclide evidence of ischemia after exercise and 7 without such evidence). BP = blood pressure; EF = ejection fraction; METs = metabolic equivalents; NS = not significant; RPP = rate-pressure product.

cise, radionuclide evidence of ischemia resolved more quickly than the electrocardiogram. More than half of the patients had no radionuclide evidence of ischemia between 1 and 3 minutes after exercise. Patients who had abnormal radionuclide angiograms after exercise had greater ischemia at peak exercise and a more prolonged recovery of the ST-segment depression after exercise. The time course of recovery of ST-segment depression and radionuclide indicators of ischemia after exercise is clearly very different.

One implication of this study is that radionuclide im-

aging at peak exercise is a more sensitive indicator of ischemia than radionuclide imaging after exercise. Although the radionuclide method used in this study is an averaging technique used over a 2-minute period with the earliest postexercise images being obtained at 1 minute after exercise, Dymond et al²³ noted similar results using the more rapid first-pass technique. Using sequential first-pass studies at rest, at peak exercise and immediately after exercise in patients without prior myocardial infarction, they found that postexercise imaging achieved a sensitivity of only 68%. Similar results

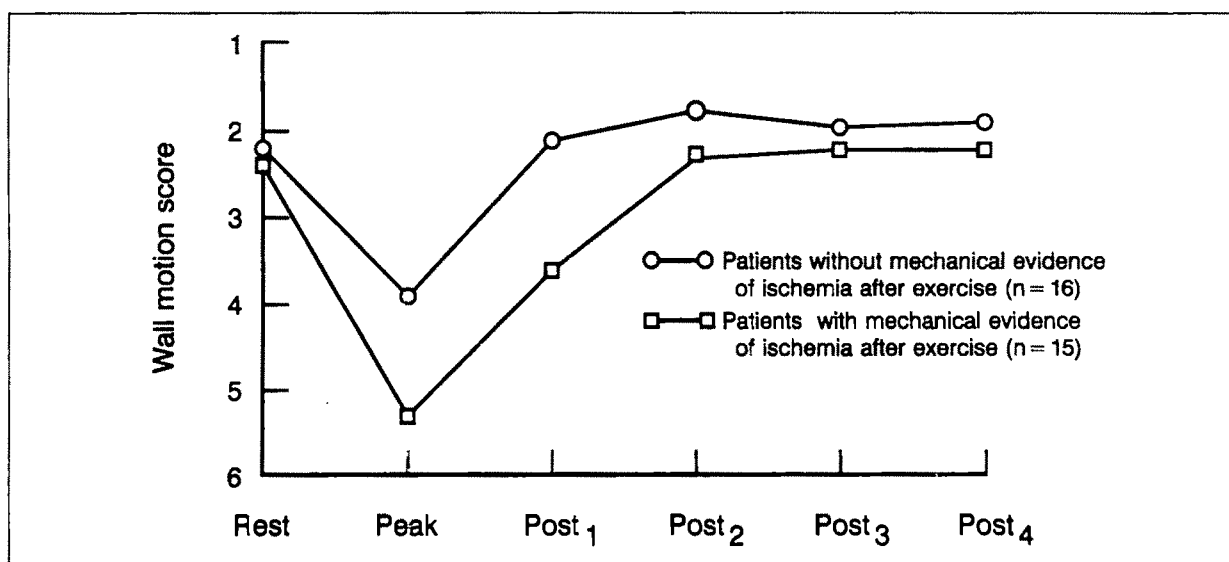


FIGURE 3. Mean wall motion score at rest, peak exercise and each postexercise (post) period. The patients were further subdivided into those with mechanical evidence of ischemia after exercise (n = 15) and those without mechanical evidence of ischemia after exercise (n = 16). Patients with mechanical evidence of ischemia after exercise had a more severe abnormality at peak exercise.

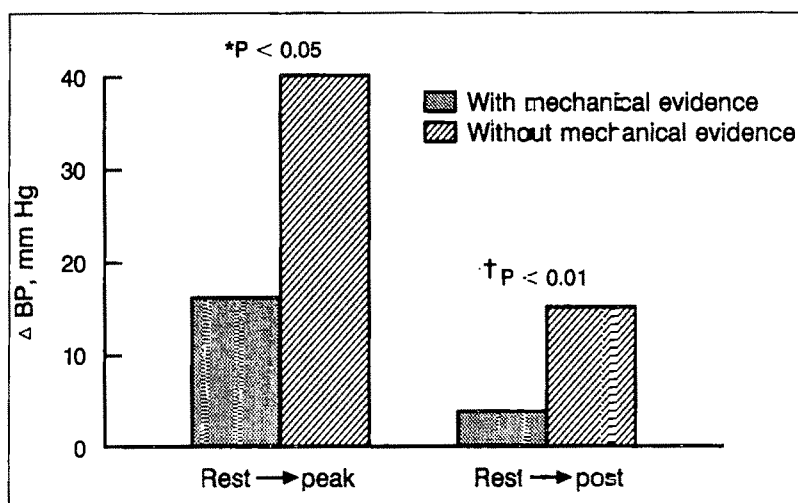


FIGURE 4. Change in systolic blood pressure (Δ BP) from rest to peak exercise and from rest to 2 minutes after exercise (post) for the 15 patients for whom post-exercise blood pressure measurements were available. The patients are subdivided into those without mechanical evidence of ischemia after exercise ($n = 7$) and those with mechanical evidence of ischemia after exercise ($n = 8$). Patients without mechanical evidence of ischemia after exercise had a greater increase in systolic blood pressure with exercise that persisted after exercise.

were found in a comparison of postexercise and transeosophageal atrial pacing using 2-dimensional echocardiography.²⁴

The rapid recovery of radionuclide evidence of ischemia after exercise does not seem to be simply a result of the decline in systolic blood pressure after exercise. Patients with abnormal radionuclide angiograms after exercise generally had a lower systolic blood pressure after exercise than at rest. These findings are in agreement with those of Schneider et al,²⁵ who found that delayed functional recovery was associated with severe coronary artery disease and was not primarily influenced by hemodynamic changes.

Among the limitations of this study are the possible effects of medication and body position. Patients receiving β -adrenergic blockers were included, and although these agents may have influenced postexercise recovery, the pattern of radionuclide recovery occurring before ST-segment depression was present both in the patients who were taking β -adrenergic blockers and in those who were not. In addition, no difference was noted in the recovery of the ST-segment changes in those patients taking β -adrenergic blockers and those who were not. These findings, obtained in the supine position, may not apply to the upright position. It should also be noted that the first postexercise image was obtained with the patient's feet up in the stirrups of the bicycle ergometer and the other 3 postexercise images were obtained with the patient completely supine. This change in position will presumably reduce ventricular volumes and systolic wall tension and thereby reduce ischemia. However, 16 of the 31 patients had no radionuclide evidence of ischemia immediately after exercise while their feet remained in the bicycle pedals.

Although consecutive patients were evaluated, patient selection did occur. To qualify for entry into the study, patients were required to have both an exercise electrocardiogram positive for ischemia and a new regional wall motion abnormality or decrease in ejection fraction during exercise. This study group was selected to prevent patients with a false-positive electrocardiogram from entering the study. Thus, the study group was selected to have true ischemia to permit comparison

of electrical ischemia (ST-segment depression) with mechanical ischemia (judged by an abnormal exercise radionuclide angiogram).

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Acute Coronary Vasomotor Effects of Nifedipine and Therapeutic Correlates in Syndrome X

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In 18 patients (12 women) presenting with effort-induced chest pain and normal coronary angiograms (syndrome X), 10 mg sublingual nifedipine increased the lumen of major coronary arteries (quantitative angiography) by $13 \pm 10\%$ ($p < 0.01$), coronary blood flow (thermodilution) by $23 \pm 26\%$ ($p < 0.05$), norepinephrine plasma concentration by $60 \pm 42\%$ ($p < 0.01$) and decreased the global ST-segment shift during the effort stress test from 8.8 ± 4.1 to 7 ± 6.8 mm ($p < 0.03$) at comparable maximal workload and at unchanged double product. There was a correlation (positive) of changes in flow with changes in coronary lumen diameter ($r = 0.65$, $p < 0.01$) with ST-segment response to exercise ($r = 0.83$, $p < 0.001$) and with (inverse) norepinephrine plasma concentration ($r = -0.70$, $p < 0.01$); no correlation was found between ST-segment response and changes in arterial lumen diameter. In a few cases, nifedipine did not improve or even worsened the response to exercise; coronary flow was unchanged or decreased and norepinephrine plasma levels were modestly or greatly increased, respectively. After 4 weeks of treatment with nifedipine (10 to 20 mg 4 times daily), the effort ST-segment shift was further decreased to 4.4 ± 3.5 mm ($p < 0.03$) despite a slightly increased double product. Plasma norepinephrine values, as compared to those after acute nifedipine, were decreased by 40% in patients with further improvement and were unchanged in patients whose exercise performance did not vary.

Thus, nifedipine improved the effort test through coronary vasodilatation rather than decrease in oxygen demand; variations in the ST shift were correlated with changes in flow and not in lumen diameter; adrenergic activation by nifedipine may, in some patients, counterbalance or even offset the coronary vasodilating efficacy of the drug; this effect attenuates with prolonged therapy. Syndrome X appears to be a disorder in coronary microvessel motility, which is sensitive to calcium-channel blockade (dilatation) as well as to norepinephrine (constriction).

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A disorder in vascular smooth muscle contractility, possibly related to abnormal intracellular calcium handling, has been detected in patients with syndrome X (effort-induced chest pain despite normal coronary angiograms).¹ This abnormality leads to enhanced vasoconstrictor response and to inadequate vasodilator reaction of the microvessels to metabolic and/or pharmacologic stimuli.^{2,3} Calcium-channel blockers appear to be a rational therapeutic approach to this syndrome. Thus far, however, clinical studies have provided conflicting results.⁴⁻⁷ We therefore investigated the short- and long-term therapeutic efficacy of calcium-channel blockade with nifedipine in patients with syndrome X and correlated it with the acute coronary vasomotor response to the same drug. In fact, it was previously shown that the vasomotor reaction to nifedipine is predictive of treatment efficacy in coronary disorders in which calcium ions may have a pathogenetic role.^{8,9}

METHODS

Patients: The study group comprised 18 patients (12 women) with a mean age of 54 ± 7 years, having normal coronary angiograms and fulfilling the following inclusion criteria: stable, effort-induced chest pain associated with positive and reproducible exercise stress test; positive Holter monitoring (>0.15 mV ST-segment depression during ordinary daily activity) and/or reversible perfusion defects on thallium-201 myocardial scintigraphy; absence of left ventricular hypertrophy (echocardiography); normally contracting left ventricle; and no nifedipine treatment in the previous 3 months.

All patients had positive responses to ≥ 2 of the tests listed previously; in 12 of 18 (60%) cases, all tests were positive. Subjects did not complain of chest pain at rest, were normotensive ($<140/90$ mm Hg) and did not present with valvular or primary myocardial diseases. Drug treatment was withdrawn ≥ 1 week before the study. Sublingual nitrates were the only medications allowed during chest pain episodes.

Study design: The study was approved by the local ethics committee and written informed consent was obtained from all patients. Diagnostic coronary angiography was carried out with the Judkins technique in multiple projections (using Siemens-Elema equipment with C-arm). Contrast medium (Iopamidol-370) was injected at a flow rate of 3 ml/s. Standard hemodynamic measurements were obtained through a 7Fr Swan-Ganz thermodilution balloon-tipped catheter (Edwards Laboratories) positioned in the pulmonary artery. Blood pressure was recorded with a 7Fr pigtail catheter positioned in the ascending aorta and advanced into the left

ventricular cavity for end-diastolic pressure recording. An 8Fr multithermistor thermodilution pacing catheter (Webster Laboratories) was introduced through the right internal jugular vein and advanced into the coronary sinus. Catheter stability was frequently checked through fluoroscopy and by iced saline injections into the right atrium to exclude blood reflux into the coronary sinus.¹⁰

Twenty minutes after coronary arteriography, systemic and coronary hemodynamics were recorded and arterial blood for norepinephrine determination was withdrawn. Nifedipine (10 mg sublingual) was then given and hemodynamic measurements and blood sampling were repeated 30 minutes after the drug. Left coronary artery angiograms were then taken again in 2 views (90° apart).

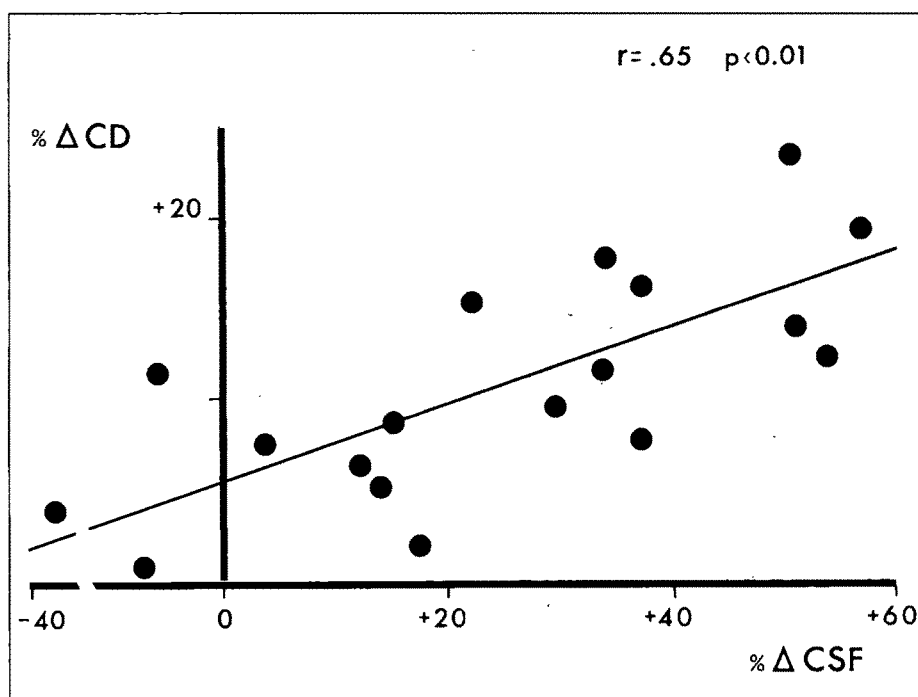
The response to treatment was assessed by exercise testing. The ergometric tests were performed in the postabsorptive state, in the upright position and on an isokinetic bicycle ergometer with a 6-channel analyzing electrocardiographic recorder (Siemens Sicard 440S). Electrocardiogram, heart rate and blood pressure (cuff manometry) were recorded every 2 minutes of exercise and at 1, 3, 5 and 8 minutes during the recovery phase. Exercise began at 150 kpm/min (25 watts) and the workload was increased by 150 kpm/min every 2 minutes. The test was continued until ST-segment depression, >2 mm with or without angina, was induced. The ST-segment shift was measured automatically at each step of exercise and during the recovery phase in 3 leads that in each patient showed the most obvious electrocardiographic alterations, so that the total value of ST-segment depression could be obtained.

Exercise stress test was performed ≥ 48 hours after coronary angiography, while patients were not taking drugs (baseline). After complete recovery from the first test, nifedipine (10 mg sublingually) was administered

and exercise test was repeated 30 minutes later (acute phase treatment). Then patients were subjected to a long-term oral regimen of nifedipine, at doses ranging from 10 to 20 mg 4 times daily, based on clinical benefits and side effects. The ergometric evaluation was performed 4 weeks later, 90 minutes after the last dose of medication (long-term treatment). Subsequently, nifedipine was replaced by placebo in 10 patients and exercise stress tests were repeated 2 weeks later. Both patients and investigators evaluating the stress tests were blinded in regard to active or placebo phases. The exercise test was maximal in the control condition and peak workload was kept constant in each patient throughout the subsequent tests. Blood samples for norepinephrine plasma values were taken before the exercise stress tests in the long-term phase of treatment while patients were in the supine position (data were available in 7 of 18 patients).

Data analysis: Coronary sinus flow was measured according to a previously described method¹¹ and coronary resistance was calculated from the ratio of aortic pressure and coronary blood flow. Quantitative angiographic measurements were automated by a validated method of digital processing.¹² Briefly, digital images were obtained by viewing each single-frame cineangiographic image with a television camera (RCA 1005 VIDICON) that served as input to a digital angiographic system (ADAC 4100 C). The computerized analysis of the coronary artery diameter was obtained by means of an interactive computer program with previous magnification of the area of interest and placement by the observer of a cursor point across normal vessel diameter. Measurements were performed in all patients at the proximal, mid- and distal-thirds of the anterior descending artery and of the left circumflex artery. A 7Fr Judkins left coronary artery catheter was taken as standard reference measurement. To assess ac-

FIGURE 1. Plot of changes of coronary sinus flow (% Δ CSF) versus changes of coronary artery diameter (% Δ CD) after 10 mg sublingual nifedipine.



curacy and reproducibility of measurements by a comparison with objects of known dimensions, we produced a digital radiographic image of a phantom of 5 silastic tubes filled with contrast medium, ranging from 0.8 to 4.9 mm. A strong linear correlation was found between the mean observed diameter versus the true diameter of the test object. The 2 independent observers who evaluated angiograms before and after the calcium antagonist were unaware of the study phase. The interobserver variability was <10%.

Plasma norepinephrine was determined by high-performance liquid chromatography with electrochemical detection.¹³

Statistical analysis: Statistical analysis of the data was performed by means of a paired *t* test. Correlations were tested with a fit linear regression analysis. Comparison of the exercise stress tests was performed by means of the analysis of variance. A *p* value <0.05 was considered statistically significant. Data are grouped as mean \pm standard deviation.

RESULTS

Systemic and coronary hemodynamic effects of nifedipine: After nifedipine, systolic blood pressure decreased from 148 ± 18 to 129 ± 13 mm Hg ($p < 0.001$), diastolic blood pressure from 83 ± 9 to 75 ± 10 mm Hg ($p < 0.001$), left ventricular end-diastolic pressure from 15 ± 5 to 12 ± 6 mm Hg ($p < 0.05$) and systemic vascular resistance from $1,392 \pm 251$ to $1,065 \pm 227$ dynes cm^{-5} ($p < 0.001$). Heart rate increased from 70 ± 10 to 82 ± 12 beats/min ($p < 0.001$) and cardiac index from 3.4 ± 0.5 to 4 ± 0.7 liters/min/ m^2 ($p < 0.001$); double product was unchanged (10.2 ± 1.2 vs 10.5 ± 2 , mm Hg \times beats/min). In addition, coronary sinus flow increased from 112 ± 47 to 139 ± 43 ml/min ($p < 0.05$) and coronary resistance decreased from 1.04 ± 0.40 to 0.74 ± 0.23 mm Hg/ml ($p < 0.01$). The left anterior descending coronary artery diameter

dilated from 2.71 ± 0.9 to 3.02 ± 0.5 mm ($p < 0.001$) and the left circumflex artery diameter increased from 2.36 ± 0.3 to 2.68 ± 0.4 mm ($p < 0.001$).

Individual percent changes from baseline control after nifedipine are listed in Table I.

These data show that the coronary vasomotor response was neither related to changes in systemic pressure and flow nor to myocardial oxygen demand (as reflected by the rate-pressure product). A positive correlation ($r = 0.65$, $p < 0.01$, Figure 1) was found between changes in coronary flow and changes in diameter of the left coronary arteries (average of variations of the left anterior descending and left circumflex artery lumen).

Plasma norepinephrine increased from 198 ± 79 to 282 ± 83 pg/ml ($p < 0.01$). These variations inversely correlated with those in coronary flow ($r = -0.70$, $p < 0.01$, Figure 2), and not with those in coronary lumen diameter ($r = -0.45$, $p > 0.1$).

Effort test response to nifedipine: The total ST-segment shift on exercise in the baseline was 8.8 ± 4.1 mm and was decreased to 7 ± 6.8 mm ($p < 0.03$) after short-term nifedipine administration and to 4.4 ± 3.5 mm ($p < 0.03$) after long-term treatment. Six out of 18 (33%) and 10 out of 18 (55%) patients showed a normal electrocardiographic response to exertion in short- and long-term evaluation, respectively. Individual electrocardiographic responses to effort test are shown in Figure 3. Changes in ST-segment shift after short-term calcium-channel blockade correlated with changes in coronary blood flow ($r = 0.83$, $p < 0.001$, Figure 4) but not with those in coronary lumen diameter ($r = 0.45$, $p > 0.1$).

The rate-pressure product at peak exercise slightly increased after both short-term (25.5 ± 6.3 vs 27.5 ± 4.5 mm Hg \times beats/min, difference not significant) and long-term nifedipine therapy (27.1 ± 4.1 mm Hg \times beats/min, difference not significant).

All patients had angina pectoris at peak exercise in

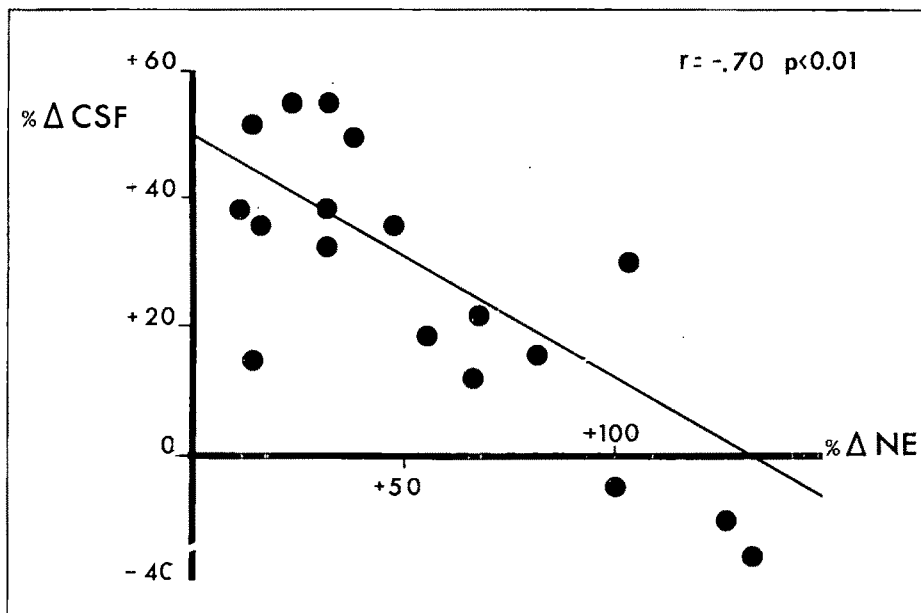


FIGURE 2. Plot of changes of coronary sinus flow (% Δ CSF) versus changes of norepinephrine plasma concentration (% Δ NE) after 10 mg sublingual nifedipine.

the untreated condition, whereas it occurred in 11 of 18 (61%) and in 6 of 18 (33%) patients after short- and long-term therapy, respectively.

Norepinephrine plasma concentration, as compared to the short-term therapy step, decreased from 279 ± 82 to 176 ± 54 in 6 patients who further improved their ST response to exercise or was unchanged (211 vs 218 pg/ml) in the single patient whose exercise performance was steady.

In the 10 patients who were switched to placebo after the active phase of treatment, both symptoms and electrocardiographic changes on exertion invariably reverted to baseline (Figure 3).

DISCUSSION

Acute vasomotion and therapeutic effects: Calcium-channel blockade with nifedipine promoted an overall moderate clinical improvement in patients with syndrome X. The mechanism underlying benefits of this drug in the presence of normal coronary angiograms is not easily understood. Coronary vasodilatation with increased blood flow has been postulated by Cannon et al.⁵ In our patients, nifedipine attenuated the anginal symptoms as well as the ST shift on effort despite a slight increase in the rate-pressure product (an index of myocardial oxygen demand).¹⁴ This suggests that the advantages of the drug may be mediated through an

FIGURE 3. Individual electrocardiographic responses to exercise (total ST-segment downsloping [mm] in baseline (B), after 10 mg sublingual nifedipine (A), after long-term nifedipine treatment (L) and after placebo (P, 10 patients). Open circles indicate patients showing a negative exercise stress test response (<1 mm ST-segment depression during exercise and/or recovery phases) after the drug. Triangles represent the means.

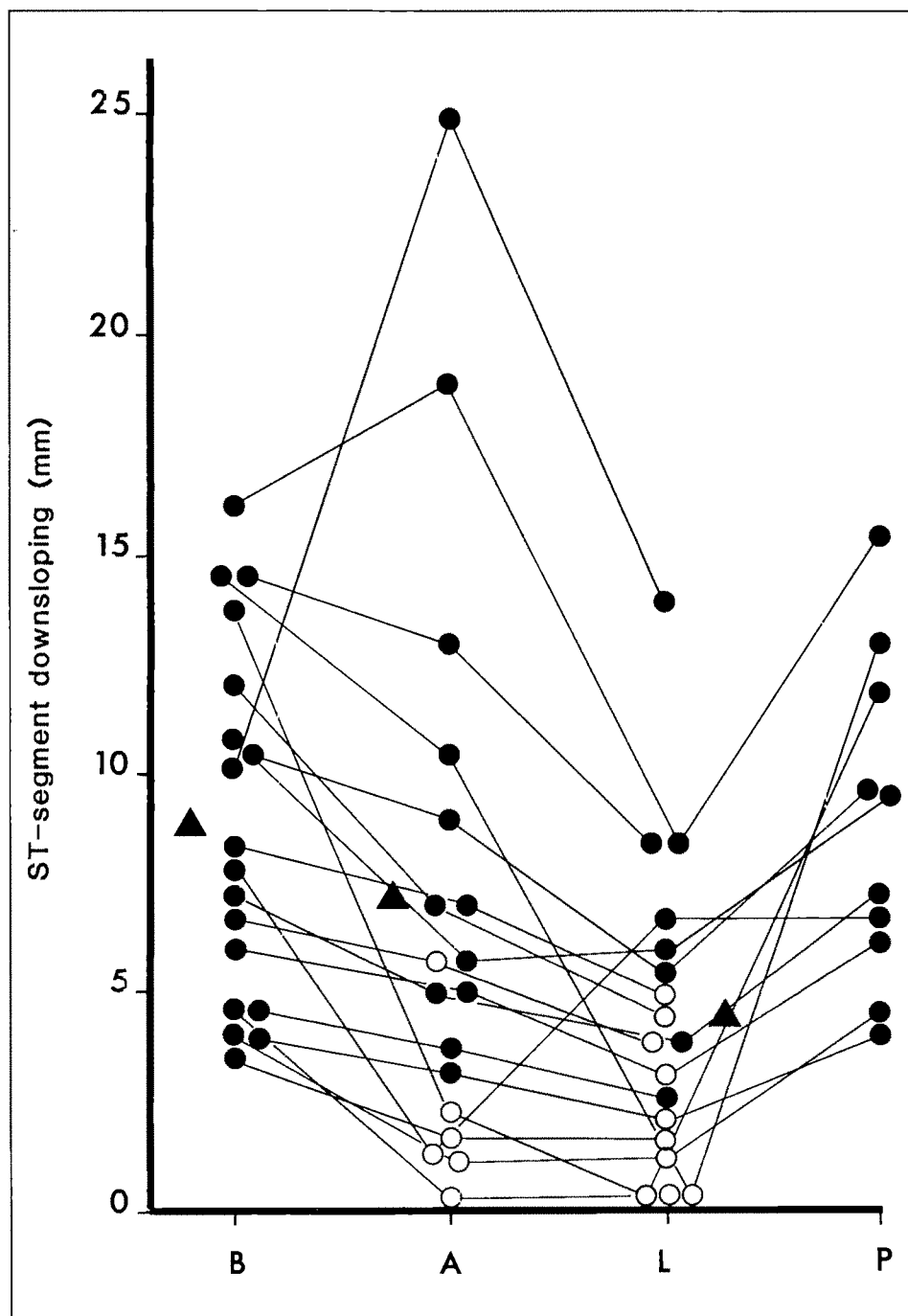


TABLE I Individual Percent Changes from Baseline After Nifedipine

	Age (yr) & Sex	HR	SBP	DBP	CI	LVEDF	SVR	DP	CF	CR	ADd	CXd	NE
1	54M	25	-17	-20	42	-7	-41	2	11	-29	12	24	72
2	51F	29	-4	0	25	-80	-21	23	52	-36	6	17	28
3	52F	7	-21	-10	-11	-37	-4	-16	39	-19	13	12	15
4	53F	24	-8	-6	24	-75	-24	14	-10	43	2	2	140
5	48F	9	-5	-11	24	-13	-26	5	37	-34	15	10	36
6	54F	-3	-17	-17	26	11	-33	-19	-7	-12	12	12	103
7	58F	15	-9	-17	-2	-23	-12	5	20	-28	13	18	72
8	56F	19	-16	-6	18	-55	-25	-14	50	-42	8	20	16
9	56F	5	-3	-10	13	-33	-18	1	30	-30	7	29	36
10	59M	5	-11	-6	13	-14	-19	-6	13	-20	17	5	15
11	50M	41	-23	-16	45	-38	-45	8	51	-47	13	36	36
12	53M	37	-12	0	34	40	-29	20	32	-33	4	28	107
13	56F	1	-12	-6	-6	-11	-2	-12	33	-33	8	-5	49
14	44F	11	-3	-7	4	0	-9	7	17	-22	4	2	60
15	49F	21	-14	-6	28	-19	-29	3	34	-34	15	5	18
16	61F	25	-14	0	18	-12	-21	8	45	-40	25	13	38
17	59M	11	-20	-13	21	-29	-31	-11	15	-29	6	5	86
18	50M	17	-11	-14	21	-27	28	4	-40	48	1	6	144
Mean	54	16	-12	-9	19	-23	-23	1	23	-22	11	14	60
± SD	7	12	6	6	15	28	11	12	26	26	6	11	42

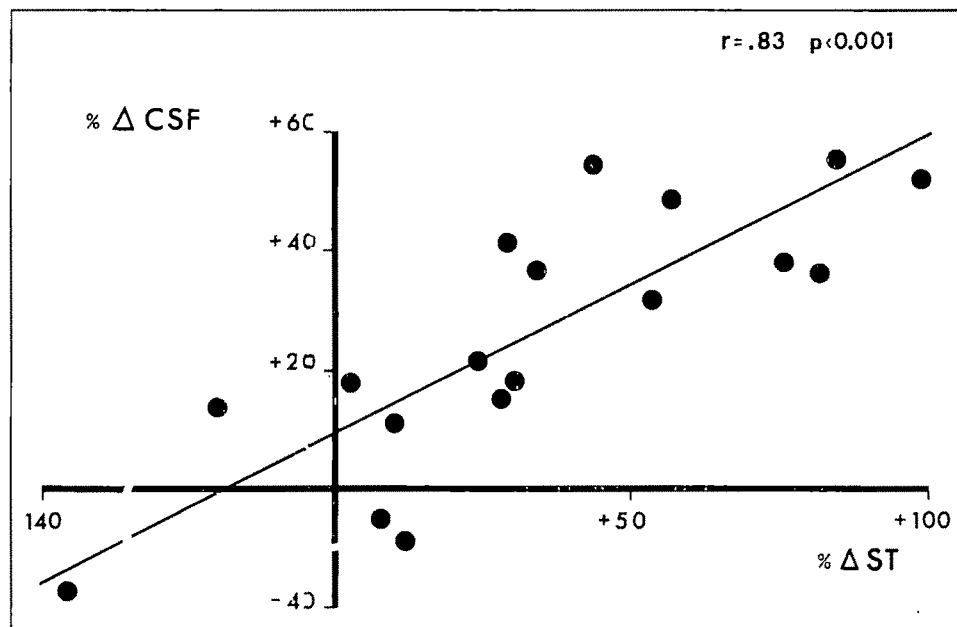
ADd = anterior descending diameter; CI = cardiac index; CF = coronary flow; CR = coronary resistance; CXd = circumflex diameter; DBP = diastolic blood pressure; DP = double product; HR = heart rate; LVEDF = left ventricular end-diastolic pressure; NE = norepinephrine; SBP = systolic blood pressure; SD = standard deviation; SVR = systemic vascular resistance.

increase in myocardial blood flow rather than through a decrease of metabolic requirements. The coronary vasomotor response to nifedipine supports this interpretation. In fact, the drug increased coronary vascular lumen and total blood flow. Moreover, there was an evident relation between the coronary flow response and the ST-segment shift during exercise. Modifications of the lumen of the great epicardial vessels, on the contrary, did not appear to be related to changes in exercise stress performance, reinforcing the concept that micro- rather than macrocirculation is disordered in syndrome X.

In a few cases, calcium-channel blockade did not improve or made worse the response to stress test. In these

cases, at equal changes in coronary perfusion pressure and double-product, coronary blood flow was unchanged or decreased, resistance was steady or increased and norepinephrine was modestly or greatly augmented. There is evidence in the literature¹⁵⁻¹⁹ that, under certain circumstances, sympathetic activation or exogenous norepinephrine may overshadow metabolic coronary vasodilation and result in an increase of resistance and a decrease of myocardial blood flow. We have also reported that a reflex sympathetic stimulation may, in some cases, counterbalance and even offset the vasodilating properties of the calcium antagonist, nifedipine, and promote coronary vasoconstriction.²⁰ In this study, changes in norepinephrine plasma levels after nifedipine

FIGURE 4. Plot of changes of coronary sinus flow (% Δ CSF) versus changes of total ST-segment shift during exercise (% Δ ST) after 10 mg sublingual nifedipine.



inversely correlated with changes in coronary blood flow, suggesting that, in the setting of an increased coronary sensitivity to constrictor influences, adrenergic factors may limit the vasodilating and the therapeutic response to calcium-antagonist treatment.

Long-term efficacy: The therapeutic efficacy of nifedipine was found further improved at the long-term evaluation. Differences in the peak exercise workload and double product did not account for this improvement. Interestingly, electrocardiographic improvement was coupled with a decrease in circulating norepinephrine, whereas a less pronounced ST shift was associated with no change in norepinephrine. This suggests that nifedipine, when given for a long period of time, attenuates or loses its capability to activate the adrenergic nervous system,^{21,22} so that the unopposed coronary vasodilating effect facilitates further clinical improvement.

Limitations of the study: The lack of a double-blind control design is an obvious limitation to the conclusions of this study. However, syndrome X still represents a heterogeneous and poorly defined clinical entity, making it hard to select an appropriate control group for angiographic evaluation. On the other hand, using each patient as his or her own control would have excessively prolonged the duration of the study. Since clinical and electrocardiographic parameters reverted to baseline in the 10 patients who were switched to placebo after completion of the active drug treatment, a therapeutic influence of nifedipine is more likely than a spontaneous variability of the disease.²³

Conclusions: Nifedipine appears to be beneficial in patients with syndrome X. A decrease in coronary tone is most likely involved in these effects; an excessive adrenergic reaction to nifedipine may limit the benefits or even be detrimental in some patients; such an occurrence tends to attenuate during long-term treatment.

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Relation Between Ventricular Late Endocardial Activity During Intraoperative Endocardial Mapping and Low-Amplitude Signals Within the Terminal QRS Complex on the Signal-Averaged Surface Electrocardiogram

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Noninvasive recording of ventricular late potentials and intraoperative endocardial mapping at 36 sites were performed in 24 patients with left ventricular aneurysm and drug-resistant sustained ventricular tachycardia due to coronary artery disease. Their mean age was 55 ± 8 years. Mean ejection fraction was $28 \pm 12\%$. For detection of late potentials on the signal-averaged QRS complex, 3 different algorithms were used. Late potentials were found in 54, 67 and 67% of the patients, respectively. In patients with a late potential on the signal-averaged electrocardiogram (ECG), delayed local activation (>40 ms beyond the QRS complex on the intraoperative surface ECG) was recorded at 5.5, 5.5 and 5.6 endocardial sites. In patients without a late potential, this type of delayed local activation was detected at 2.4, 1.1 and 0.9 of 36 endocardial sites, respectively ($p < 0.05$; $p < 0.01$; $p < 0.002$). The mean delay of local endocardial activity was 38, 35 and 37 ms in patients with a late potential on the body surface recording versus 20, 19 and 11 ms, respectively, in patients without a late potential ($p < 0.05$; $p < 0.05$; $p < 0.002$). There was no correlation between the duration or amplitude of the late potential, if present, and the number of endocardial sites exhibiting delayed activity ($r = -0.23$, $r = -0.05$, $r = 0.21$; correlation not significant for each) or the mean duration of the endocardial delayed activity ($r = -0.25$, $r = -0.14$, $r = -0.07$; correlation not significant for each). These results indicate that the presence of late potentials on the signal-averaged surface ECG is related to the mean duration of endocardial late activity as well as to the number of endocardial sites exhibiting a given degree of delayed activation. Thus, it is dependent on the mass of slowly activated tissue. However, a direct conclusion from the duration or the amplitude of a late potential to the amount of delayed activation or the extent of endocardial time delay does not seem possible.

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Ventricular late potentials represent low-amplitude activity that can be recorded from areas of previous myocardial infarction in patients with and without documented ventricular tachycardia.^{1,2} These potentials represent electrical activity from areas of slow conduction and predispose to reentrant tachyarrhythmias.³ Ventricular late potentials that can be recorded from the body surface using appropriate recording techniques are supposed to represent electrical activity originating from these areas. However, there is a paucity of data comparing direct intraoperative or catheter-mapped endocardial recordings from the area of the previous myocardial infarction to late potentials at the body surface. Therefore, the aim of this study was to correlate the results of direct intraoperative recordings of late activity from this area to low-amplitude signals on the signal-averaged electrocardiogram (ECG). The detection of late potentials on the body surface using the signal-averaging technique may be influenced by unstable triggering and inconstant noise level. Another determinant is the algorithm used to define the presence of a late potential.⁴ Despite the similarity of the morphologic appearance of low amplitude signals as recorded with the various systems, the final results of analysis may be different depending on the algorithms used.⁵ Therefore, we used 3 different algorithms to detect late potentials on the signal-averaged surface ECG.

METHODS

Patients: Twenty-four patients with chronic recurrent sustained ventricular tachycardia or ventricular fibrillation, or both, were studied. Mean age was 55 ± 8

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years. Nineteen patients were men. All patients had a left ventricular aneurysm after previous anterior wall infarction. In 10 patients, the occlusion of the left anterior descending coronary artery was the only location of coronary artery disease. In another 10 patients, 2-vessel disease was present with the right coronary artery as well as the ramus circumflexus, each being involved in 5 cases. The remaining 4 patients exhibited 3-vessel disease. Mean angiographically determined ejection fraction from a right anterior oblique view was $28 \pm 12\%$. The median number of previous defibrillations was 3 (range 0 to 10). In all patients, sustained ventricular tachycardia could be induced during the baseline electrophysiologic study. The mean cycle length of the induced ventricular tachycardia was 332 ± 72 ms. The induction of sustained ventricular tachycardia was achieved during basic drive by single premature stimuli in 3 cases and by double premature stimuli in the remaining cases. To allow intraoperative localization of the site of origin of ventricular tachycardia by programmed stimulation, patients did not receive antiarrhythmic drugs, while 2 patients still had significant antiarrhythmic blood concentrations after cessation of amiodarone therapy.

Coronary angiography and biplane left ventriculography were performed to establish the nature of the underlying cardiac disorder. The baseline electrophysiologic study was performed using 3 to 4 multipolar electrode catheters that were introduced percutaneously and posi-

tioned under fluoroscopy, as reported in detail previously.^{6,7}

Intraoperative endocardial mapping was performed in the area of the previous myocardial infarction using the recording system previously described.^{8,9} A multipolar reference electrode was sutured to the anterior wall of the right ventricle. After instituting normothermic cardiopulmonary bypass, local endocardial electrical activity was recorded through an incision in the center of the left ventricular aneurysm. All recordings were done using a tripolar, hand-held probe with an interelectrode distance of 1.5 mm. The tripolar hand-held probe was moved clockwise for 3 circles around the endocardial surface of the anterior wall aneurysm. The circle closest to the incision was considered as circle I whereas the circle at the borderline to the macroscopically identified normal myocardium was considered as circle III. The "clockface" orientation used the base of the heart as 12 o'clock. Local signals were recorded from 12 sites on each of the 3 circles, yielding a total number of 36 sites. The following signals were recorded using an 8-channel, direct-writing, ink-jet recorder (Siemens-Elema, Mingograph): lead I and III, the bipolar signal from the multipolar reference electrode, and 3 bipolar signals from the tripolar hand-held probe as well as a time-reference signal. The onset of a bipolar signal was taken at the point where the upstroke from the baseline reached an angle of 45° as suggested by Scherlag et al.¹⁰ All recordings were placed on a Hewlett-Packard 9111 A graphics

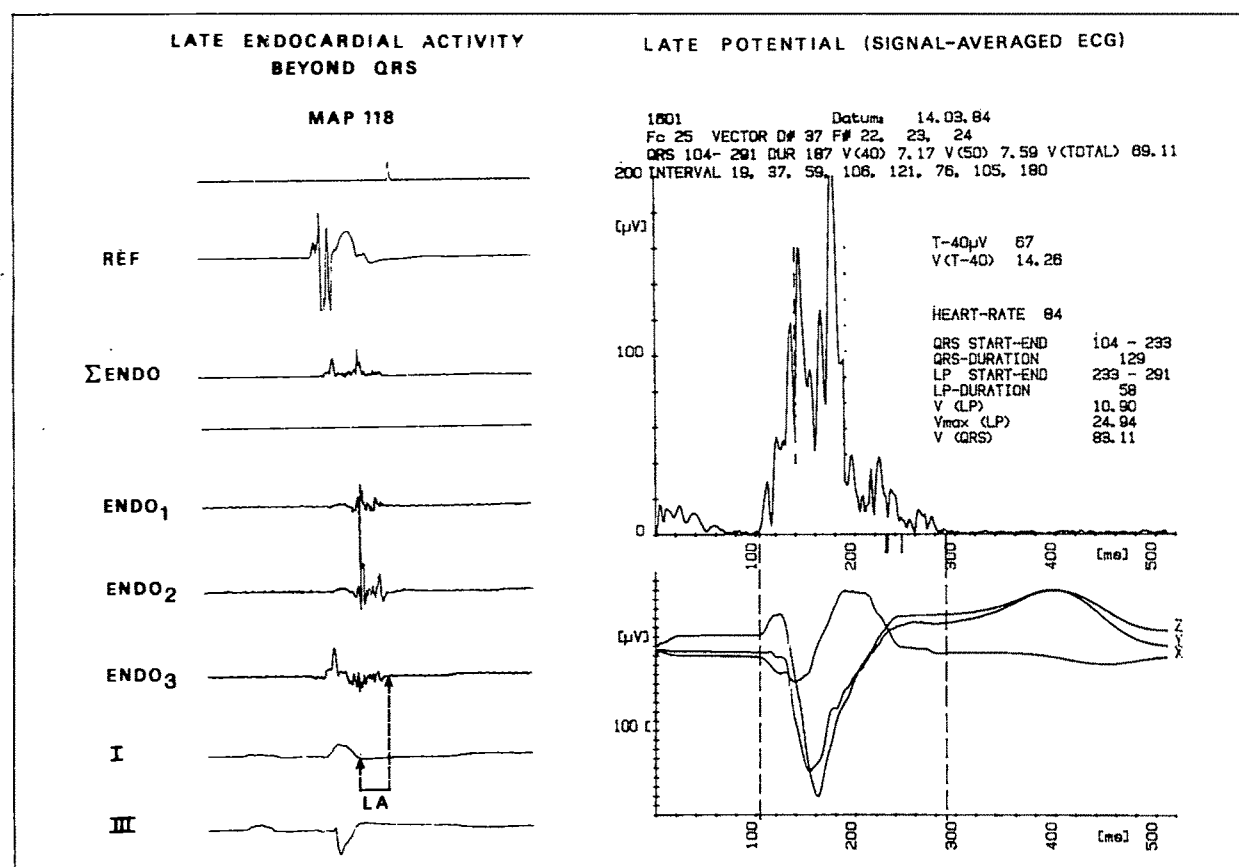


FIGURE 1. Comparison between endocardial late activity and a noninvasively recorded late potential on the signal-averaged electrocardiogram in the same patient. Endo = endocardial lead; LA = delayed endocardial activity.

TABLE I Late Potentials on the Signal-Averaged ECG (3 different algorithms) and Delayed Endocardial Activity

Pt	Late Potential on Signal-Averaged ECG			Delayed Endocardial Activity in Intraoperative Mapping	
	Definition (1) $V_{(40)}$ (μ V)	Definition (2) T-40 μ V (ms)	Definition (3) LP duration (ms)	LA _{>40 ms} Sites (n)	Mean LA Duration (ms)
	No LP	No LP	No LP		
1*	No LP	No LP	No LP	0	13
2	No LP	No LP	No LP	0	8
3	No LP	No LP	No LP	0	14
4	No LP	No LP	No LP	0	18
5	No LP	No LP	No LP	4	27
6	No LP	No LP	No LP	3	21
7	No LP	No LP	No LP	0	9
8*	No LP	No LP	18	2	42
9	No LP	30	19	2	13
10	No LP	35	25	2	22
11	No LP	31	27	13	40
12	24	32	No LP	0	7
13	22	30	25	2	108
14	21	39	24	3	28
15	20	38	31	7	40
16	19	38	37	7	43
17	11	61	39	16	50
18	10	116	32	2	21
19	7	56	49	10	40
20	7	67	58	9	38
21	5	52	42	3	29
22	5	52	42	5	21
23	4	55	36	5	25
24	4	105	70	2	36

* After cessation of antiarrhythmic therapy.
 LA_{>40 ms} = local late-endocardial activity for >40 ms beyond the end of QRS; mean
 LA = mean duration of endocardial delayed activity beyond QRS; LP = late potential;
 V = voltage; T = time.
 For details of definitions, see text.

tablet for further analysis. Points of interest were identified as described below and digitized using a specially written program on a Hewlett-Packard 9826 computer. The data of at least 3 consecutive cycles were measured and averaged. The following definitions were used for the endocardial recordings (Figure 1): (1) the duration of the local endocardial signal, i.e. the interval between the onset and the end of the local signal; (2) the duration of the surface QRS complex in lead I and III (i.e., the interval between the earliest onset and the latest end at each site of recording); and (3) the local delayed activity (i.e., that part of the local signal that extends beyond the end of the QRS complex on the intraoperative surface ECG).

Signal-averaging was performed in all patients before undergoing surgery. For recording and subsequent processing of the signals obtained from the orthogonal ECG leads (X,Y,Z), the software program developed by Simson¹¹ was implemented on a Hewlett-Packard desktop computer (model 9826). Signal averaging was performed during normal sinus rhythm. Typical noise level was 0.7 μ V. At least 50 beats were averaged.

The following parameters were evaluated (high pass filter setting 25 Hz): (1) the voltage in the terminal 40

ms of the signal-averaged and filtered QRS complex: $V_{(40)}$ ¹¹; (2) the time backwards from the end of the signal-averaged and filtered QRS complex to the point in time where the signal exceeded 40 μ V during retrograde analysis: T-40 μ V¹²; and (3) the duration of the late potential as estimated by a specially designed algorithm that detected the transition point between high-amplitude and low-amplitude signals within the terminal QRS complex. The duration of a late potential was then defined by the time measured from this point to the point where the signal again reached the isoelectric line: LP duration.¹³

A late potential was considered to be present if one of the following definitions was true: definition (1): $V_{(40)} < 25 \mu$ V; definition (2): T-40 μ V ≥ 30 ms; or definition (3): LP duration > 10 ms.

Statistical analysis: For comparison of endocardial data in patients with and without a late potential on the signal-averaged surface ECG, statistical analysis was performed by the Wilcoxon's test for unpaired observations. The relation of endocardial data to the duration or amplitude of late potentials, if present, was analyzed by linear regression analysis.

RESULTS

Signal-averaging of the surface ECG and intraoperative endocardial mapping were performed in all 24 patients. A typical example of the results of endocardial recording versus the signal-averaged ECG is shown in Figure 1. The data are listed in Table I.

Signal-averaging: Late potentials were found in 13 patients (54%) using definition (1), in 16 patients (67%) using definition (2) and in 16 patients (67%) using definition (3). Any of these definitions was met in 17 of 24 patients (71%). The lower incidence of late potentials compared to other studies may be due to the predominantly high rate of ventricular tachycardia.

Intraoperative mapping: Endocardial local late activity was found in all patients. The mean number of sites at which late activity was recorded was 16 ± 9 . Late activity exceeding the QRS complex for > 10 ms was found at 10.4 ± 7.3 sites and for > 20 ms at 7.8 ± 6.6 sites. Endocardial late activity lasting > 30 ms after the end of the QRS complex was found at 5.2 ± 5.2 endocardial sites and lasting for > 40 ms beyond the end of the QRS complex at 4.0 ± 4.3 sites, respectively. Local delayed endocardial activity exceeding the end of the QRS complex for > 50 ms was only found at 2.4 ± 2.9 sites.

Relation between intraoperatively recorded local late endocardial activity and signal-averaged electrocardiogram: The number of sites at which endocardial activity exceeded the end of the QRS complex was not significantly different in patients with and without late potentials on the signal-averaged ECG. This was also the case if the number of sites with endocardial activity exceeding the end of the QRS complex by > 10 or 20 ms, respectively, was correlated to the presence or absence of late potentials. In contrast, the number of endocardial sites with local activity that exceeded the end of the QRS complex by > 30 ms was significantly greater

TABLE II Differences in Number of Sites With Delayed Endocardial Activity of a Given Degree in Patients With and Without Late Potentials on the Signal-Averaged ECG, Respectively (3 different algorithms)

	No. of Sites with Delayed Activity (patients with versus without late potential)					
	any	>10 ms	>20 ms	>30 ms	>40 ms	>50 ms
Definition (1)	ns	ns	ns	ns	<0.05	<0.05
Definition (2)	ns	ns	ns	<0.05	<0.01	ns
Definition (3)	ns	ns	ns	<0.02	<0.002	<0.05

in patients with late potentials compared to those without for definition (2) ($p < 0.05$) and definition (3) ($p < 0.02$). Local delayed endocardial activity appearing >40 ms after the end of the QRS complex was found at more sites of recording in patients with than in patients without late potentials in the signal-averaged ECG in-

dependent of the definition used (Figure 2). In detail, patients who met definition (1) had delayed activity lasting for >40 ms after the end of the intraoperatively recorded QRS complex at 5.5 ± 4.4 sites whereas, in the remaining patients, delayed activity was found at only 2.4 ± 3.8 sites ($p < 0.05$). Using definition (2), this type of delayed activity (>40 ms after QRS) was recorded at 5.5 ± 4.5 sites in patients with but at only 1.1 ± 1.6 sites in patients without late potentials ($p < 0.01$). Patients with late potentials based on definition (3) presented delayed local activity for >40 ms after QRS at 5.6 ± 4.3 sites versus 0.9 ± 1.6 sites in those without ($p < 0.002$). The number of sites with delayed activity >50 ms after the end of QRS was correlated to the presence of late potentials with respect to definition (1) ($p < 0.05$) and definition 3 ($p < 0.05$) but not for definition (2) (difference not significant for each) (Table II). The lack of correlation in the latter instance may be due to the fact that long delays of this duration were rare. In

FIGURE 2. Number of sites exhibiting local endocardial late activity for >40 ms beyond the intraoperatively recorded surface electrocardiogram in patients with (dotted bars) and without (white bars) a late potential on the signal-averaged electrocardiogram, as based on the 3 different definitions used.

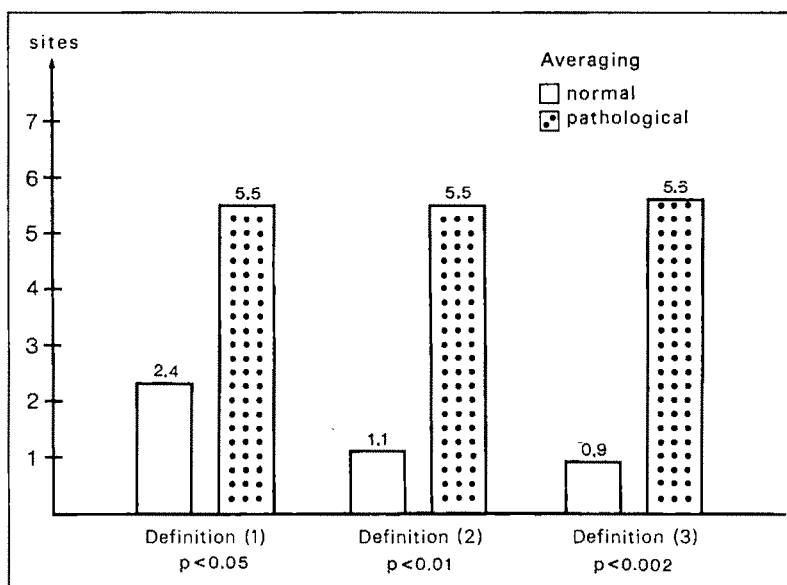
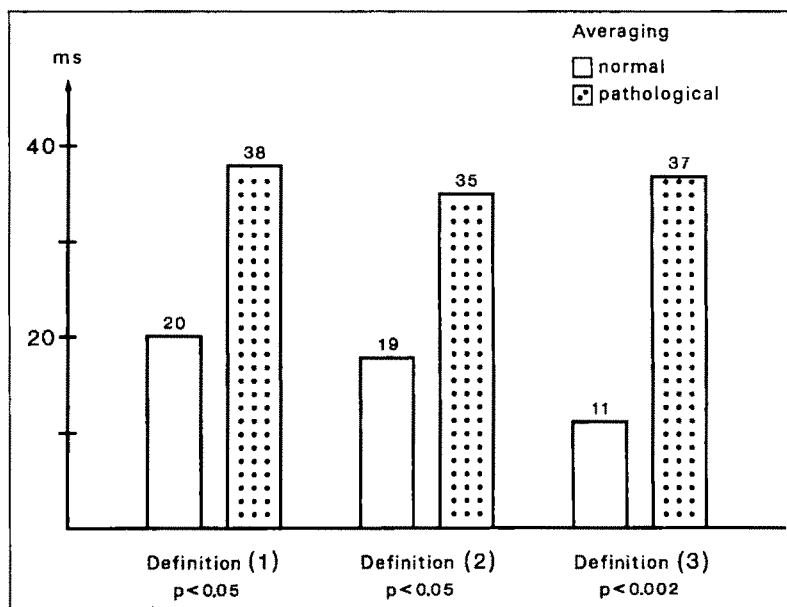


FIGURE 3. Mean duration of endocardial activity in patients with (dotted bars) and without (white bars) a late potential on the signal-averaged electrocardiogram, as based on the 3 different definitions used.



patients with late potential following definition (1), the mean duration of local late activity was 38 ± 25 ms compared to 20 ± 12 ms in patients without ($p < 0.05$). Following definition (2), the mean duration of endocardial late activity was 35 ± 23 ms. In patients who did not meet this definition, the mean endocardial delay was 19 ± 11 ms ($p < 0.05$). Using definition (3), the mean duration of the endocardial delay was 37 ± 21 ms in patients with a late potential versus 11 ± 7 ms in patients without ($p < 0.002$) (Figure 3).

However, there was no correlation between the duration or amplitude of a late potential, if present, and the number of sites exhibiting local late endocardial activation (definition (1), $r = -0.23$; definition (2), $r = -0.05$; definition (3), $r = 0.21$, correlation not significant for each) (Figure 4). There was also no correlation between the measured duration or amplitude of the late potential and the mean delay of local late endocardial activation (definition (1), $r = -0.25$; definition (2), $r = -0.14$; definition (3), $r = -0.07$, correlation not significant for each) (Figure 5).

DISCUSSION

Low-amplitude fractionated signals after the terminal QRS complex can often be recorded by signal-averaging techniques in patients with coronary artery disease after previous myocardial infarctions. Low-amplitude fractionated endocardial activity was also detected in epicardial registrations in animal models,^{3,14-17} as well as during endocardial catheter mapping and intraoperative epicardial registrations in man.^{2,18-24} Since there is only limited information available on the correlation between direct intraoperative recordings of delayed endocardial activity from the area of previous myocardial infarction and late potentials on the signal-averaged ECG, the aim of this study was to compare both approaches.

We report 2 major findings. First, the presence of late potentials was correlated to the number of sites with endocardial local delayed activity beyond a given degree as well as to the mean duration of endocardial late activity. Second, the amplitude or duration of a late potential, if present, was not correlated to the number of

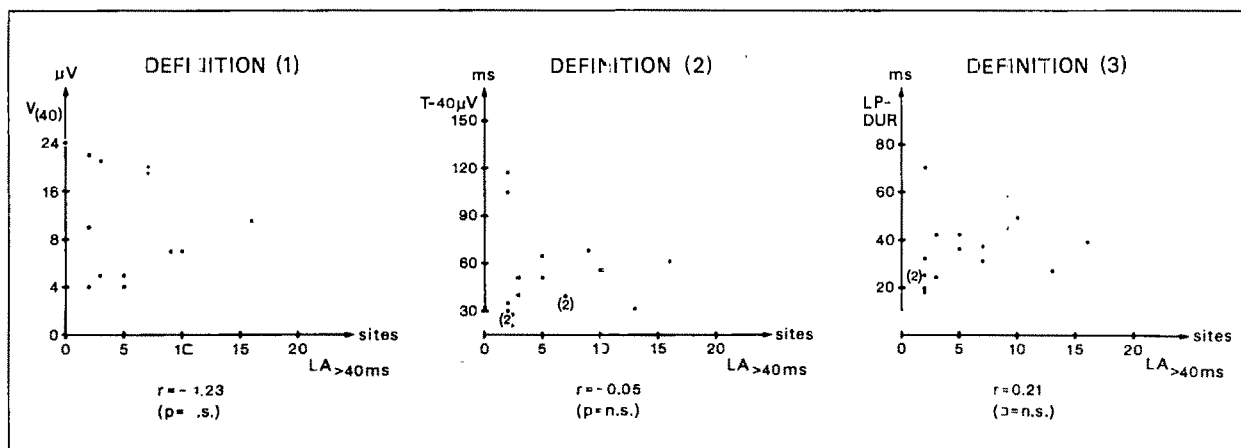


FIGURE 4. Correlation between number of endocardial sites exhibiting local late endocardial activity extending beyond the QRS complex in the intraoperatively recorded surface electrocardiogram for >40 ms ($LA > 40$ ms) and the duration or amplitude, respectively, of the late potentials on the signal-averaged electrocardiogram (3 different algorithms). LP-DUR = late potential duration.

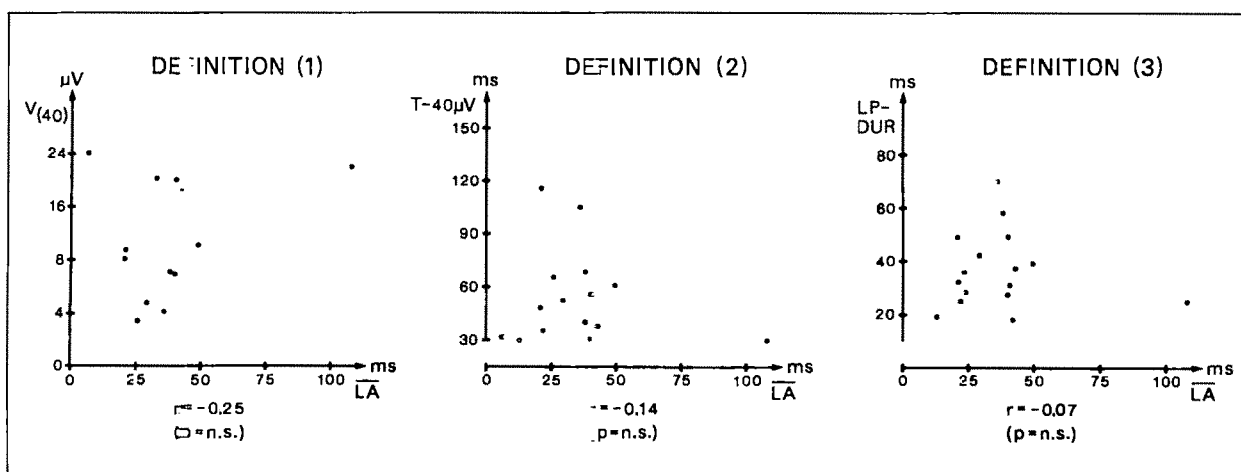


FIGURE 5. Correlation between the mean duration of endocardial late activity beyond the intraoperative recorded surface electrocardiogram and the duration or amplitude, respectively, of late potentials on the signal-averaged electrocardiogram (3 different algorithms). Abbreviation as in Figure 4.

delayed activated endocardial sites or to their mean delay.

Local endocardial late activity may exceed the end of the signal-averaged QRS complex at a given site of recording to varying degrees.^{2,21} This was also shown in this study, since the duration of local activity at some endocardial sites of recording was definitely longer than that on the body surface ECG. An explanation may be that signal-averaging leads to cancellation of at least part of the signal due to jitter of the trigger point, filter attenuation or the presence of undulating levels of noise.^{4,25} Although this cannot be ruled out on the basis of the present study, an alternative explanation may be more probable. The good correlation between the presence of late potentials on the signal-averaged ECG with the number of sites exhibiting a given degree of local endocardial delay leads to the conclusion that the detection of a late potential depends not only on the duration of delayed activity but also on the mass of abnormal myocardial tissue activated with a given delay. This is supported by the animal experiments showing that mass was a critical factor for the detection of delayed activated myocardial tissue at the body surface.¹⁷

Simson et al² studied the relation between late potentials at the body surface and directly recorded fragmented electrograms in 8 patients with and 11 patients without ventricular tachycardia. All patients had left ventricular endocardial catheter maps. Patients with a late potential on the signal-averaged ECG exhibited a significantly higher percentage of fractionated endocardial electrograms during the last 40 ms of the signal-averaged QRS complex (68 vs 17%, $p < 0.001$). In the patients, who were operated upon, epicardial mapping was performed. Fragmented electrograms were rarely found during intraoperative epicardial mapping. If present, they were found exclusively within areas of previous infarction. In a subsequent report from the same group, Vassallo et al²¹ obtained signal-averaged ECGs and endocardial catheter mapping in 41 patients with coronary artery disease and sustained ventricular tachycardia. Patients with signal-averaged late potentials had a significantly greater number of sites of late activity during catheter mapping of the left ventricle. These were later and longer in duration than in patients without late potentials on the signal-averaged ECG.

Miller et al²⁶ studied 50 patients with anteroapical left ventricular aneurysms due to prior myocardial infarction at the time of aneurysmectomy. Forty-four of these patients had inducible ventricular tachycardia during intraoperative electrical stimulation. These patients exhibited more fractionated electrograms than the remaining 6 patients without inducible ventricular tachycardia (20 ± 14 vs $9 \pm 7\%$ of electrograms; $p < 0.04$). The investigators concluded that differences between groups of patients with versus without inducible ventricular tachycardia exist that are more quantitative than qualitative in nature. The present study also documented a relation between the duration of local delayed activity and the presence of late potentials. In patients with a late potential on the signal-averaged surface

ECG, the mean endocardial delay was significantly longer than in patients without it.

Several possibilities have been discussed to evaluate a correlation between the duration or amplitude of a late potential on the signal-averaged surface ECG and the delayed endocardial activation areas. In this study, we could not find any significant correlation between the delayed endocardial activation and the duration or amplitude of a late potential, if such was present. This may be due to the registration techniques used. However, it seems to be more probable that parts of the endocardial signals are too low in amplitude, or the mass of tissue is too small to allow the recording of its delayed activity on the body surface or even at the epicardium. This explanation is supported by the finding that already epicardial registrations of fragmented signals do not necessarily correspond to the endocardial registration.¹⁹ This would also explain the observation made by Simson et al,² who found 88% of fractionated signals in the endocardial recordings even though more epicardial than endocardial sites were sampled.

All these reports as well as the present study show that the presence of a late potential is significantly related to the duration as well as to the amount of delayed endocardial activity. However, neither the amplitude nor the duration of a late potential allows a direct conclusion to the mass or the mean delay of endocardial late activity.

Limitations: Due to the limited registration time during cardiopulmonary bypass, the areas mapped were restricted to 36 predetermined endocardial sites, which is certainly this study's main limitation. To obtain a maximum of information about the zone of primary interest, we preferred to focus on the area of the previous myocardial infarction instead of mapping the whole left ventricle or including epicardial sites, which would have decreased the information about the target area to a degree most probably insufficient to provide the performed type of analysis. This may have underestimated the extent of delayed endocardial activation, especially with regard to the macroscopical identification of this area. However, the fact that in all patients the circle at the borderline to normal tissue indeed showed predominantly normal activation patterns suggests a quite complete examination of the zone of interest. The high amount of information from the area of previous myocardial infarction is certainly the main advantage of this type of analysis. This is also true compared with endocardial catheter mappings, which often fail to get a sufficient great number of predetermined endocardial sites in this area. Additionally, endocardial catheter mapping can only be performed in patients with tachycardias providing a sufficiently stable hemodynamic situation, which leads to a certain patient selection. Focussing on the area of previous myocardial infarction might also explain that, contrary to other investigators^{2,21} who also examined potentially normal areas, we found a comparatively large number of sites exhibiting endocardial late activity. Another limitation is due to the changes in amplitude and morphology of the QRS complex after tho-

racotomy and especially after ventriculotomy. This causes changes in the amplitude and duration of the QRS complex in the extremity leads, which may appear shorter than with all 12 leads available. This may have slightly overestimated the duration of local delayed activity.

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Studies of Left Ventricular Dysfunction (SOLVD)—Rationale, Design and Methods: Two Trials That Evaluate the Effect of Enalapril in Patients with Reduced Ejection Fraction

The SOLVD Investigators*

The Studies of Left Ventricular Dysfunction (SOLVD) is an extensive program of research that has 3 components. (1) Two large double-blind randomized trials evaluate the effects of enalapril on mortality, morbidity and quality of life of patients with left ventricular (LV) dysfunction with overt congestive heart failure (CHF) (Treatment Trial in 2,500 patients) and without overt CHF (Prevention Trial in 4,600 patients). (2) Seven detailed sub-studies evaluate the effect of enalapril on a number of intermediate outcomes such as right and LV function and hemodynamics, LV mass and wall stress, hormones, arrhythmias, exercise capacity and quality of life in subsets of patients in the 2 large trials. (3) Finally, a registry of 6,336 patients with congestive heart failure or LV dysfunction is designed to describe the clinical course of an unselected group of patients. The rationale and design of a tiered approach to clinical trials that are large enough to provide reliable information on mortality and morbidity, yet provide relevant information on other endpoints, are described.

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*See Appendix.

Congestive heart failure (CHF) is a major and increasingly recognized public health problem. It has been estimated that approximately 2 million Americans have CHF and approximately 250,000 new cases are diagnosed each year.¹ Moreover, since the prevalence is known to increase with age, increases in the average life expectancy would be expected to result in a higher prevalence of patients over the next few decades.¹ The mortality among CHF patients is reported to be between 10 and 20%/year, so that about 200,000 to 400,000 deaths/year can be attributed to CHF in the US. Worldwide the number of deaths may be between 1 and 2 million/year.

The recognition that patients with CHF often have elevated peripheral vascular resistance has led to the introduction of vasodilator therapy, which has emerged as an important component of its treatment. Of the vasodilators, the angiotensin-converting enzyme (ACE) inhibitors appear to be the most promising, since they counteract some of the major adverse hormonal and vasoconstrictor mechanisms, relieve symptoms, diminish cardiac dilatation after myocardial infarction² and improve exercise capacity and ejection fraction in short-term (<3 months) controlled, randomized, double-blind studies.³

In 1985 little was known about the impact of any long-term drug treatment on survival. An overview⁴ of several small short-term randomized trials of ACE inhibitors suggested a favorable trend toward a lower mortality but the data were too limited to allow reliable conclusions. Consequently, the Studies of Left Ventricular Dysfunction (SOLVD) were designed chiefly to address this issue. Since the design of SOLVD, the results of 2 new studies have become available.

The Cooperative North Scandinavian Enalapril Survival Study⁵ was a randomized double-blind trial evaluating the effect of enalapril on patients with severe CHF (New York Heart Association functional class IV despite the use of other therapy). This trial was stopped after only 253 of the 400 planned patients were enrolled because of a significant decrease in 6-month mortality in the enalapril group. There were 68 deaths among 126 placebo patients compared to 50 among 127 in the enalapril group (a 27% risk reduction, 95% confidence intervals of 4 to 44%, $p < 0.003$). It is likely that the study was stopped at a time when the results were exagger-

TABLE I Exclusion Criteria

Participant Eligibility and Exclusion Criteria, Screening and Prerandomization Visits

Medical history of intolerance to enalapril.
 Prospective participant already receiving an ACE inhibitor and unable to discontinue.
 Myocardial infarction in the last 30 days. (This is only a temporary exclusion.)
 Hemodynamically significant primary valvular or outflow tract obstruction (e.g., mitral valvular stenosis, aortic valvular stenosis, asymmetric septal hypertrophy or malfunctioning prosthetic valve).
 Constrictive pericarditis.
 Complex congenital heart disease.
 Syncopal episodes presumed to be due to life-threatening arrhythmias (asymptomatic cardiac arrhythmias including ventricular tachycardia are not an exclusion criterion).
 Any prospective participant in whom cardiac surgery including transplantation is likely in the near future (e.g., participant's name is on cardiac transplant list). In particular, if a potential participant is likely to need CABG surgery in the immediate future, he/she should be excluded but can be reassessed for eligibility after surgery.
 Unstable angina pectoris (defined as angina at rest) or severe stable angina (more than an average of 2 attacks/day) despite treatment.
 Uncontrolled hypertension at the time of randomization (uncontrolled blood pressure is defined as systolic blood pressure >140 mm Hg AND diastolic blood pressure >95 mm Hg).
 Cor pulmonale (right ventricular failure secondary to pulmonary disease).
 Advanced pulmonary disease ($FEV_1/FVC = \leq 50$, peak expiratory flow rate <200 ml/s, $FVC < 60\%$ of predicted).
 Major neurologic diseases that could lead to early death (i.e., Alzheimer's disease, advanced Parkinson's disease).
 Cerebrovascular disease (e.g., significant carotid-artery stenosis) that could potentially be complicated or rendered unstable by administration of an ACE inhibitor. (Prospective participants who may be at increased risk for stroke should their blood pressure decrease excessively. The mere presence of a carotid bruit need not in itself exclude participants.)
 Collagen vascular disease other than rheumatoid arthritis (i.e., systemic lupus erythematosus, polyarteritis nodosa, scleroderma).
 Suspected significant renal artery stenosis.
 Renal failure (i.e., creatinine >2.5 mg/dl or dialysis patients).
 Malignancies, except for surgically cured skin cancer, carcinoma-in-situ, or 5 years free of disease after the diagnosis of solid tumors.
 Requirement for immunosuppressive therapy. (The use of steroids for non-life-threatening diseases such as arthritis is not an exclusion.)
 Active myocarditis.
 Significant primary liver disease.
 Likelihood of a prospective participant being nonadherent due to chronic alcoholism, lack of a fixed address, drug addiction, etc.
 Other life-threatening disease or prospective participant who is not realistically expected to be discharged alive from the hospital.
 Pregnant woman or woman of child-bearing potential who is not protected from pregnancy by any method.
 Prospective participant who is simultaneously receiving other investigational drug protocols (other than for compassionate use).
 Failure to give consent.

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; FEV_1 = forced expiratory volume 1; FVC = forced vital capacity

ated, so that it is possible that the real effect may well be more modest. In this trial only 194 patients were followed up to 6 months and only about 102 beyond 1 year. Further, the proportion of deaths after the first 3 months appeared to be similar in the enalapril and control groups. Therefore, data on long-term effects of ACE inhibitors on mortality when administered beyond about 6 months are lacking, particularly in patients who are mildly symptomatic or asymptomatic.

In the Veterans Administration Vasodilator Heart Failure Trial⁶ a lower mortality was observed when hydralazine and isosorbide dinitrate rather than placebo were added to digoxin and diuretic therapy in patients with class II and III CHF. Since only 459 patients were randomized to these treatment arms, the mortality difference was not statistically significant ($p = 0.93$). No benefit was observed in the group randomized to prazosin compared to placebo. Thus, although this study is suggestive of a favorable effect of some vasodilators on survival, confirmation in further studies is required.

The SOLVD was designed in 1984 and 1985 and initiated in 1986 primarily to evaluate the effects of enalapril, an ACE inhibitor, on long-term mortality and major morbidity in a broad group of patients with LV dysfunction. Two important considerations have influenced the design of SOLVD. (1) It is possible that drug treatment given to patients who already have manifest CHF may not be as beneficial as initiating treatment at

an earlier stage of the disease (e.g., in patients with asymptomatic LV dysfunction). Conversely, early treatment of such asymptomatic patients may be less beneficial, as the patients may not have measurable activation of the renin-angiotensin axis. Therefore, examination of the effects of treatment separately in these 2 categories of patients was considered to be desirable. (2) Given the general experience with various agents in heart disease, where even very promising interventions appear to have only a moderate effect on survival, it would be prudent to expect only moderate (15, 20 or at best 25%) but not large (40 to 50%) reductions in the risk of death.⁷ Because a beneficial treatment is likely to be prescribed for the patients' "life time," whether tolerance occurs during long-term therapy needs evaluation.⁸ Therefore, 2 concurrent but separate large and long-term trials were planned: a "Prevention Trial" that would include patients with a low ejection fraction and no history of overt CHF; and a "Treatment Trial" that would include patients with a low ejection fraction and signs of overt CHF, each trial having sufficient power to detect moderate mortality reductions of about 20%.

STUDY DESIGN

The primary objective of SOLVD is to answer 2 questions: (1) (Prevention Trial) In patients with LV dysfunction (resting ejection fraction ≤ 0.35) and *no history of overt CHF*, can long-term survival be im-

proved by taking enalapril? (2) (Treatment Trial) In patients with LV dysfunction (resting ejection fraction ≤ 0.35) and with a history of overt CHF, can long-term survival be improved by taking enalapril?

To address these 2 questions, 2 separate clinical trials are being conducted in 23 medical centers. A secondary but important key analysis is the effect of treatment on survival in all participants in the study (Treatment and Prevention Trials combined). In addition, the effect of treatment will be assessed in 5 subgroups: (1) tertiles of plasma sodium (lower sodium levels reflect greater activation of the renin-angiotension axis; therefore, the effect may be greatest in this subgroup); (2) participants using versus those not using a vasodilator at baseline (patients receiving non-ACE inhibitor vasodilator may have a smaller benefit); (3) tertiles of baseline ejection fraction (patients with the lowest ejection fraction may benefit most); (4) etiology (coronary artery disease, hypertensive heart disease and other) (in patients with coronary artery disease, occurrence of ischemic events that are not affected by treatment will tend to dilute the benefit); and (5) by New York Heart Association functional classification (this was added after the results of the Cooperative North Scandinavian Enalapril Survival Study were known). In addition to these analyses, the effects of treatment on a number of other outcomes will be evaluated. Copies of the detailed protocols of the main trials, specific substudies, and registry can be provided upon request.

To investigate the effect of treatment on a variety of mechanisms or other outcomes that might mediate the benefit of enalapril treatment in the 2 trials, 7 substudies are being conducted. In selected centers, patients are entered into these substudies, which require specialized testing at repeated intervals. This philosophy of an overall simple and large study⁹ and several small but detailed substudies overcomes some of the problems of previous clinical trials (i.e., not being large enough to answer the mortality questions reliably or not being truly detailed enough to shed light on mechanisms of action). Additionally, to characterize the clinical course of a relatively unselected group of patients, a simple registry of patients with an ejection fraction ≤ 0.45 or a diagnosis of CHF, examined during a 12-month period at 18 of the 23 centers, has been maintained. Many of these registry patients are not entered into the SOLVD trials. Long-term follow-up of this group will offer a broader perspective on the factors that affect the clinical course of a less restricted population than the patients randomized into the trials.

Participants: The 2 basic criteria for entry into the trials are: (1) age between 21 and 80 years, inclusive, and (2) LV ejection fraction ≤ 0.35 , performed within 3 months of the day of consent. Ejection fraction is assessed by 1 of 3 techniques: (1) radionuclide LV angiography; (2) LV contrast angiography; and (3) 2-dimensional echocardiography with ejection fraction calculated by the area length method or Simpson's rule. Exclusion criteria are listed in Table I and fall into several broad categories: non-cardiac diseases likely to limit long-term survival, certain cardiac conditions other than

primary myocardial dysfunction, intolerance to enalapril and a substantial likelihood of nonadherence to the assigned medication.

Study size: The study aimed to enroll 2,500 patients in the Treatment Trial and 4,600 patients in the Prevention Trial. These estimates were calculated from a model using the normal approximation to the binomial distribution, with adjustment for lack of adherence to assigned treatment. The following assumptions were used: (1) a 1-sided significance level of 0.025; (2) power of 90%; (3) a 3-year mortality of 32% in the control group in the Treatment Trial (16, 8 and 8% in the first, second and third years of follow-up, respectively) (these mortality assumptions were derived from the Coronary Artery Surgery Study registry data, which showed a 3-year mortality of 50% among CHF patients with an ejection fraction ≤ 0.35 ; because trials tend to exclude some of the sickest patients, the event rates were arbitrarily reduced by one-third, for an overall 3-year mortality of 32%; in a trial with a 3-year recruitment and a further 2-year follow-up, the expected duration of average follow-up would be about 3.5 years if recruitment were uniform; however, since recruitment in most trials shows a lag in the earlier period, we compensated by assuming that follow-up would average only 3.0 years); (4) a 3-year mortality of 17% in the control group in the Prevention Trial (10.2, 3.4 and 3.4% in the first, second and third years of follow-up, respectively) (data on similar patients from the Coronary Artery Surgery Study registry indicated a 20% 3-year mortality); (5) a 25% reduction in mortality given 100% adherence with treatment; (6) a 3-year adherence proportion of 80% (non-compliance of 10% in the first year, 5% in each of the second and third years in each of the treatment arms) in the Treatment Trial and 85% in the Prevention Trial (5% noncompliance/year for 3 years); and (7) non-adherers revert to event rates of the other treatment group.

The latter 2 assumptions lessen the apparent reduction in mortality to 19% in the Treatment Trial and to 20% in the Prevention Trial. Using the above assumptions, the study size calculated for the Treatment Trial was 2,100 and that for the Prevention Trial 4,000. To protect against unexpectedly lower event rates or poorer adherence, the study sizes were inflated to 2,500 and 4,600, respectively. Therefore, if the trials are combined, the study has 90% power to detect a 13% reduction in mortality by treatment.

Ethics and informed consent: The final protocol was approved by the independent Data and Safety Monitoring Board and the Institutional Review Boards at each of the participating centers. At the first clinic visit, the objectives and overall design of the study and the risks and benefits of participation are explained carefully to each patient and written consent is obtained.

Test dose and placebo run-in: Inclusion of many patients who do not adhere to the treatment allocation can substantially decrease the power of the trial. Nonadherence may be due to inability to tolerate the active medication if the patient was allocated to the active group, urgent need for enalapril if allocated to the placebo

group or inability to comply with the protocol. It is anticipated that a small number of potential participants may develop clinically significant hypotension or other side effects after enalapril that would preclude long-term use of this drug; therefore, each participant is given 2.5 mg enalapril twice daily at the first clinic visit. A telephone call is placed to each participant 24 hours later to ensure that there are no major adverse reactions to the drug. After 2 to 7 days of receiving the medication, the participants are seen in clinic. If serious side effects develop or if a participant takes <75% of the prescribed dose and is therefore considered to be non-compliant, the participant is excluded from further consideration.

Each participant is also given placebo for 2 weeks. If the participant does not take at least 80% of the prescribed medication, the participant is excluded from further consideration. However, if in the opinion of the clinic staff there were unusual circumstances that may have led to the poor adherence, the participant may be given a second 2-week supply of placebo and reevaluated. No participant is given a third opportunity. The identity of both the test dose and placebo are known to the clinic staff but not to the patients (single blind).

Classification into Prevention or Treatment Trial: The Prevention Trial is composed of participants who do not have a history of overt heart failure. These participants have little or no limitation of exercise tolerance

due to dyspnea or fatigue and do not require treatment with digitalis, diuretics or vasodilators for heart failure at entry into the trial. The participants in the Prevention Trial belong to 1 of 2 groups: (IA) participants with ejection fraction ≤ 0.35 and who are not receiving digitalis or diuretics, or (IB) participants with ejection fraction ≤ 0.35 and who require digitalis or diuretics for problems other than heart failure (e.g., supraventricular arrhythmia and hypertension).

The Treatment Trial is composed of participants with a history of overt CHF, that is, participants who have currently or have had in the past clear clinical evidence of CHF and who currently require treatment with diuretics or inotropic drugs or vasodilators, or a combination of these, for symptomatic relief. The participants in the Treatment Trial can be viewed as belonging to 1 of 2 groups: participants with ejection fraction ≤ 0.35 and who require digitalis or diuretics for heart failure, or participants with ejection fraction ≤ 0.35 and who require non-ACE inhibitor vasodilators (usually in addition to digitalis or diuretics) for CHF.

Randomization: After the completion of the prerandomization run-in periods, participants are allocated to the enalapril or placebo groups using a permuted block randomization within each of the clinical centers. Both trials are double-blind and only the statistical coordinating center has direct access to the randomization codes.

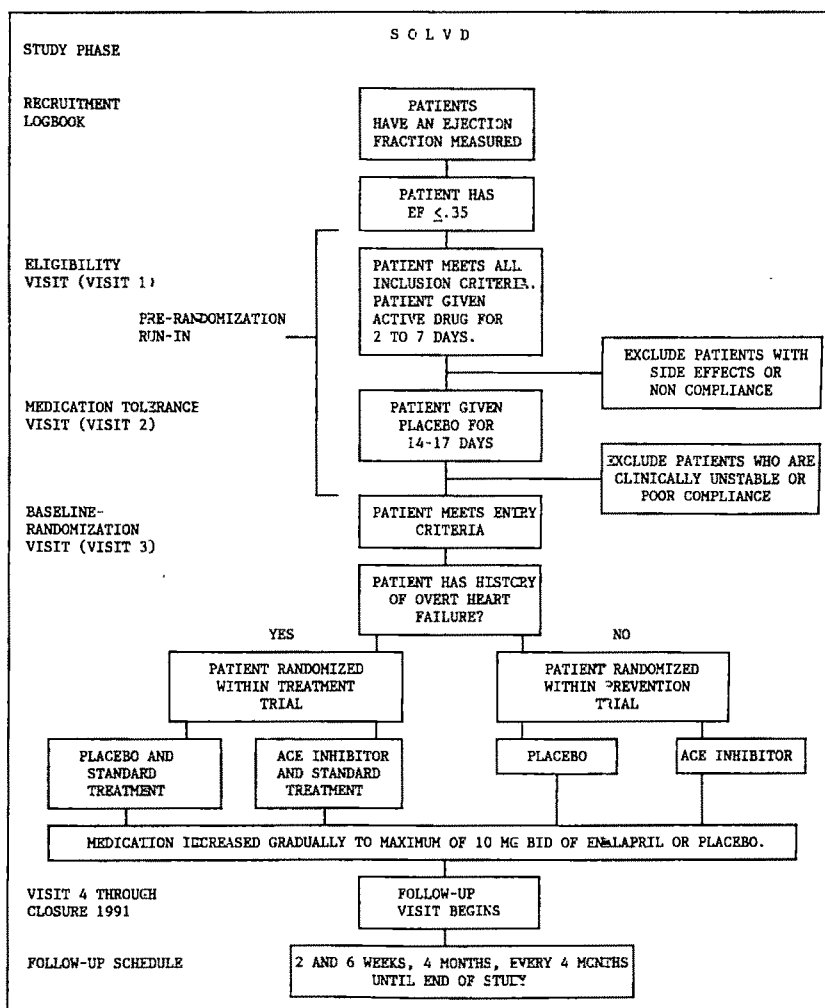


FIGURE 1. Flow diagram of Studies of Left Ventricular Dysfunction (SOLVD) clinic visits. ACE = angiotensin-converting enzyme; EF = ejection fraction.

TABLE II Summary of SOLVD Substudies

Name	Prerandomization Drug Challenge*	Study Schedules			Expected Study Size		No Participating Centers
		Baseline	4 Months	12 Months	Prevention	Treatment	
Invasive diastolic function†	—	+	—	+	25	25	1
Echocardiographic‡	+	+	+	+	200	200	5
Exercise	—	+	+	+	200	—	5
Neurohormones†‡	—	+	+	+	200	100	17
Radionuclide biventricular function†	+	+	+	+	100	50	3
Arrhythmia‡	+	+	+	+	250 (500)§	250 (500)§	10
Quality of life	—	+	+	+	200	200	5

* Evaluations conducted before and after short-term therapy before randomization.

† Studies linked to each other with patients overlapping.

‡ Studies linked to each other with patients overlapping.

§ Baseline data only in 500 patients.

SOLVD = studies of left ventricular dysfunction.

Each center's pharmacy is provided with sealed envelopes containing the treatment assignment of each participant for use in the event of an emergency that requires immediate unmasking of an individual's drug assignment.

Follow-up visit schedule: Follow-up visits are scheduled at 2 and 6 weeks after randomization and then at 4, 8 and 12 months. Thereafter, clinic visits are scheduled at 4-month intervals. Participants are contacted by telephone at least once between visits to ascertain if any study "event" has occurred and to encourage adherence.

Medication: At randomization most participants are given 5 mg of enalapril or its placebo twice daily. However, if the physician feels that the patient may have difficulty tolerating this dose, treatment is initiated at 2.5 mg twice daily. Two weeks after randomization, the participant is seen in clinic, and if the medication is tolerated, the dose is increased to 10 mg twice daily (or 5 mg twice daily). In general, physicians are encouraged to maintain patients at 10 mg twice daily. However, if patients are unable to tolerate this, the dose can be reduced.

Concomitant: Interventions other than enalapril are not restricted by the protocol and treating physicians are free to modify all other medications. However, if the use of non-ACE inhibitor vasodilators is not clearly indicated, an attempt is made to discontinue these medications during the prerandomization period. If after randomization CHF develops or worsens, the treating physician is encouraged to use diuretics, digitalis or non-ACE inhibitor vasodilators at optimal levels before considering the use of open-label ACE inhibitors.

Outcome measures: The primary outcome of interest for each trial is all-cause mortality. Subsidiary outcomes for both trials are cardiovascular mortality, sudden death, death due to worsening CHF, incidence of hospitalization for CHF, myocardial infarction, stroke, need for cardiac transplantation and quality of life. In the Prevention Trial, onset of CHF is an additional outcome of interest.

Substudies: Seven substudies are being conducted among subsets of the participants in both trials. These are (1) diastolic function substudy, (2) echocardiogra-

phy substudy, (3) exercise substudy, (4) neurohumoral substudy, (5) quality of life substudy, (6) radionuclide substudy and (7) sudden death substudy. The design, study visits and numbers of patients and clinics are listed in Table II.

ORGANIZATIONAL STRUCTURE

Clinical centers: The 23 clinical centers for SOLVD are widely distributed and include 2 in Canada and 1 in Belgium (Appendix). Each clinical center consists of a group of 1 to 8 hospitals (total of 92). A microcomputer-based distributed data management system is used, with each center entering, editing and correcting its own data forms. Data are transmitted electronically on a weekly basis to the coordinating center. The principal investigators from the clinical centers and coordinating center and the project officer constitute the study Steering Committee, which oversees all of the scientific and logistic aspects of the study.

Coordinating center: In addition to participating in the Steering Committee, the Coordinating Center has responsibility for designing, revising and distributing the forms and procedural instructions used throughout the study, implementing and monitoring the data management system and monitoring the clinical centers to ensure that the protocol is properly carried out. The Coordinating Center is responsible for receiving, editing, storing and analyzing all data from the clinical centers. The Coordinating Center prepares statistical reports of results for the Data and Safety Monitoring Board.

Project office: The Project Office is in the Clinical Trials Branch of the National Heart, Lung, and Blood Institute. It provides the scientific and administrative direction of the study. It awards and monitors contracts and in conjunction with the Steering Committee defines standards for study unit performance and ensures compliance with these standards.

Drug supply and distribution center: Merck Sharp and Dohme Pharmaceutical Company manufactures, packages and distributes both the active medication and the placebo for SOLVD. The company has no access to any other part of the study data except recruitment statistics and requirements of study drugs at each center.

Data and Safety Monitoring Board: The Data and Safety Monitoring Board, consisting of independent experts in cardiology, epidemiology, bioethics and biostatistics, has been appointed by the Director of the National Heart, Lung, and Blood Institute. This committee reviewed the protocols of the trials and the substudies before their initiation and periodically monitors the data for outcomes, toxicity and safety. The Board makes recommendations to the Director of the National Heart, Lung, and Blood Institute whether changes should be made in the conduct of the trials.

DETAILS OF DATA COLLECTION

Prerandomization: Potential participants are identified by reviewing past medical records, the logbooks of invasive and noninvasive laboratories and referrals by private physicians (Figure 1). Once a potential participant has been identified and permission to contact the participant is given by the primary physician, the participant is invited to the clinic for further evaluation.

The eligibility visit is designed to confirm that the potential participant meets the inclusion criteria for the trials. Eligible participants enter a prerandomization run-in phase, described earlier. Approximately 1 week after receiving a 2.5 mg dose of enalapril, the participants are seen in clinic for a second time. At this time any adverse symptoms are noted and investigated. Blood is drawn to determine hematocrit, white cell counts, creatinine and electrolyte levels, and the urine is tested for the presence of protein. Participants who do not tolerate the medication may be excluded or may be rescreened after appropriate modification of ancillary drug therapy. In addition, noncompliant participants are excluded. Participants who remain eligible for 1 of the trials are given a 2-week supply of placebo (again, single-blind) and a third visit is scheduled 2 weeks later.

At the third visit, if the participant has shown adequate adherence to the placebo, is clinically stable and still meets all of the criteria for entry into 1 of the 2 trials, the participant is randomly assigned to receive either placebo or enalapril.

Postrandomization: Data concerning side effects of and adherence to study treatment, discontinuation or change in study drug dosage, use of nonstudy medications and hospitalizations are collected at each visit without knowledge of the treatment assignment. The study physician determines whether there has been a change in the severity of CHF (in patients in the Treatment Trial) or new onset of CHF (in patients in the Prevention Trial) since the last visit. If a patient has been hospitalized, additional data regarding primary and secondary discharge diagnoses are recorded. A quality of life questionnaire is completed at the 6-week and 1- and 2-year visits.

Death classification: Immediately after the ascertainment of a participant's death, this fact is entered into the clinical center's microcomputer. The clinical center then obtains information concerning the death and on the basis of all available clinical information determines the cause of death using a standardized form, without knowledge of treatment assignment.

Study period: Recruitment for the study is planned for 3 years with minimum follow-up for 2 years. Thus, the total duration of the study is 5 years. Recruitment began in July 1986 and the planned study termination date is July 1991. Because recruitment to the Treatment Trial was completed 6 months ahead of schedule, this study is scheduled to be terminated in February 1991.

Data analysis: The primary analysis to determine the effect of enalapril on mortality will be based on the logrank statistic.¹⁰ Confirmatory analysis adjusting for other covariates will be accomplished through the use of standard survival analysis techniques such as the proportional hazards model.¹⁰ To assess whether treatment effect differs in various subgroups of patients, tests of interaction using the proportional hazards model will be conducted.

The Data and Safety Monitoring Board meets twice a year and reviews the data on efficacy and safety. To ensure that the overall α level at the end of the study is less than the designed 0.025, appropriate monitoring rules are used in these interim analyses. The procedure of Lan and DeMets¹¹ with a spending rule similar to the boundary of O'Brien and Fleming,¹² the boundary of Peto et al¹³ and conditional power¹⁴ are all computed and reviewed by the Data Safety Monitoring Board at its meetings.

Registry: The patients entering the SOLVD trials are likely to represent a truncated subset of the total population of patients with LV dysfunction or CHF. This is because patients having the worst and best prognosis are expected to be excluded. To study the clinical course of a broader group of patients, a registry aiming to enroll 6,000 patients has been implemented. The primary objective of the registry is to study the influence of a number of patient characteristics on mortality.

Eighteen of the 23 SOLVD centers are participating in the registry. Patients are eligible for participation if they have an ejection fraction ≤ 0.45 or a radiologically confirmed discharge diagnosis of CHF during the recruitment period. Patients are excluded if they have non-valvular congenital heart disease, any non-cardiac life-threatening disease, lack of reliable means for follow-up or if they do not consent to participation in the study. Baseline information includes identifying and demographic information, clinical history, physical examination, ejection fraction, etiology of disease, x-ray, medications used, electrocardiogram, and laboratory results.

The baseline registry data are obtained from abstraction of medical records. However, this might lead to biases due to a disproportionately greater number of investigations being performed in sicker patients. To quantify and correct for these biases, complete information is obtained on all key data and additional investigations are performed in a randomly chosen subgroup of registry participants who are seen in clinic. A detailed history is obtained and physical examination is performed. They also have blood drawn for renin, catecholamines, arginine vasopressin and atrial natriuretic factor, and undergo a 2-dimensional echocardiogram, chest x-ray and electrocardiogram. They undergo a 6-minute

walk test¹⁵ and a 70-minute ambulatory Holter monitoring.

Vital status and hospitalizations will be determined at 1 year by mail and telephone; 3- and 5-year vital status will be determined by periodic searches of national death registries.

Current status of the study: By the end of May 1990, over 4,200 patients had been randomized to the Prevention Trial and 2,568 patients had been randomized to the Treatment Trial. Recruitment to the registry of 6,336 patients and 1 year follow-up on all of these patients were completed by May 1990.

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APPENDIX

SOLVD Investigators

European Clinics

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Radial Arterial Pressure Measurements May Be a Poor Guide to the Beneficial Effects of Nitroprusside on Left Ventricular Systolic Pressure in Congestive Heart Failure

Gerald J. Simkus, MD, and David H. Fitchett, MD

The effect of nitroprusside on pressure wave transmission from ascending aorta to radial artery was studied in 10 patients with severe congestive heart failure. Nitroprusside resulted in a beneficial increase in cardiac index, reduction of pulmonary wedge pressure and reductions of aortic and radial arterial mean pressures. In 6 patients with an identifiable late systolic peak of aortic pressure (group I), nitroprusside reduced aortic systolic pressure more than radial systolic pressure, resulting in an increase in the difference between aortic and radial systolic arterial pressure (group I control 13 ± 4 , nitroprusside 20 ± 6 mm Hg; $p < 0.025$). Yet in 4 patients in whom no aortic late systolic pressure wave was apparent (group II), nitroprusside did not alter the difference between aortic and radial systolic pressures. Radial arterial pressure is often used to estimate the effect of nitroprusside on the arterial pressure load on the left ventricle. These results indicate that a reduction of radial systolic pressure induced by nitroprusside may underestimate the true reduction of aortic systolic pressure and thus the effect of the vasodilator on the arterial load on the left ventricle. The enhanced difference between aortic and radial arterial systolic pressures appears to be the consequence of nitroprusside on arterial pressure reflections.

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Radial arterial pressure is often used as a measure of the pressure developed by the left ventricle in clinical studies of vasodilator therapy. Although systolic peripheral arterial pressure is known to be higher than central aortic pressure,¹ it is usually assumed that the difference between the central and peripheral pressures remains constant during treatment with the vasodilator.

Reflected pressure waves are responsible for the augmentation of systolic pressure as the pressure wave travels from the ascending aorta to the periphery.² Furthermore, reflected waves may contribute to peak aortic systolic pressure, when wave velocities are sufficiently rapid to permit reflections to return during systole.³ Vasodilator agents not only reduce mean arterial pressure, but may also reduce pulsatile pressure by increasing arterial compliance and either delaying or reducing reflected waves.² Consequently, vasodilators such as nitroprusside could alter transmission of the pressure wave from central to peripheral arteries by changing both the amplitude and timing of vascular reflections. The present study investigates the effect of nitroprusside on arterial pressure transmission between the ascending aorta and radial artery in patients with cardiac failure, to determine whether vasodilator-induced changes of radial arterial systolic pressure are a reliable estimate of ascending aortic (and thus left ventricular) systolic pressure.

METHODS

Patients: Ten patients were evaluated. Their ages ranged from 23 to 67 years (mean 49). Each had heart failure of at least 6 months' duration and New York Heart Association dyspnea grade III or IV and were receiving standard medical treatment for cardiac failure (digoxin 9, furosemide 9, captopril 5). The etiology of the cardiac failure was ischemic heart disease (7), idiopathic dilated cardiomyopathy (2) and sarcoidosis (1). Left ventricular ejection fractions were between 7 and 22% (mean $13 \pm 4\%$).

Routine hemodynamic and angiographic studies were performed as part of an evaluation for cardiac transplantation. The patients gave written informed consent for the study, which had been approved by the Ethics Committee of the Royal Victoria Hospital.

Procedure: After completion of the diagnostic study an 18 gauge catheter was inserted percutaneously into the left radial artery, and connected by a 5 cm tube to a

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Gould disposable pressure transducer. The damped natural frequency of the system, determined at the completion of the procedure by the "pop" technique,² was between 20 and 50 Hz. A Millar SPC 484A microtip catheter was positioned in the ascending aorta. The fluid pressure recorded from the lumen of the catheter was used as a reference to check for zero drift of the microtip transducer. The level of the external transducers and

the radial artery catheter were adjusted to midchest level. Pressures were recorded using an Electronics for Medicine DR12 recorder and on electromagnetic tape.

Control data were recorded at least 20 minutes after administration of contrast medium. Nitroprusside was started at 0.5 $\mu\text{g}/\text{kg}/\text{min}$ and the dose increased until aortic systolic pressure was reduced to <85 mm Hg (average infusion rate $1.6 \pm 0.9 \mu\text{g}/\text{kg}/\text{min}$). Measure-

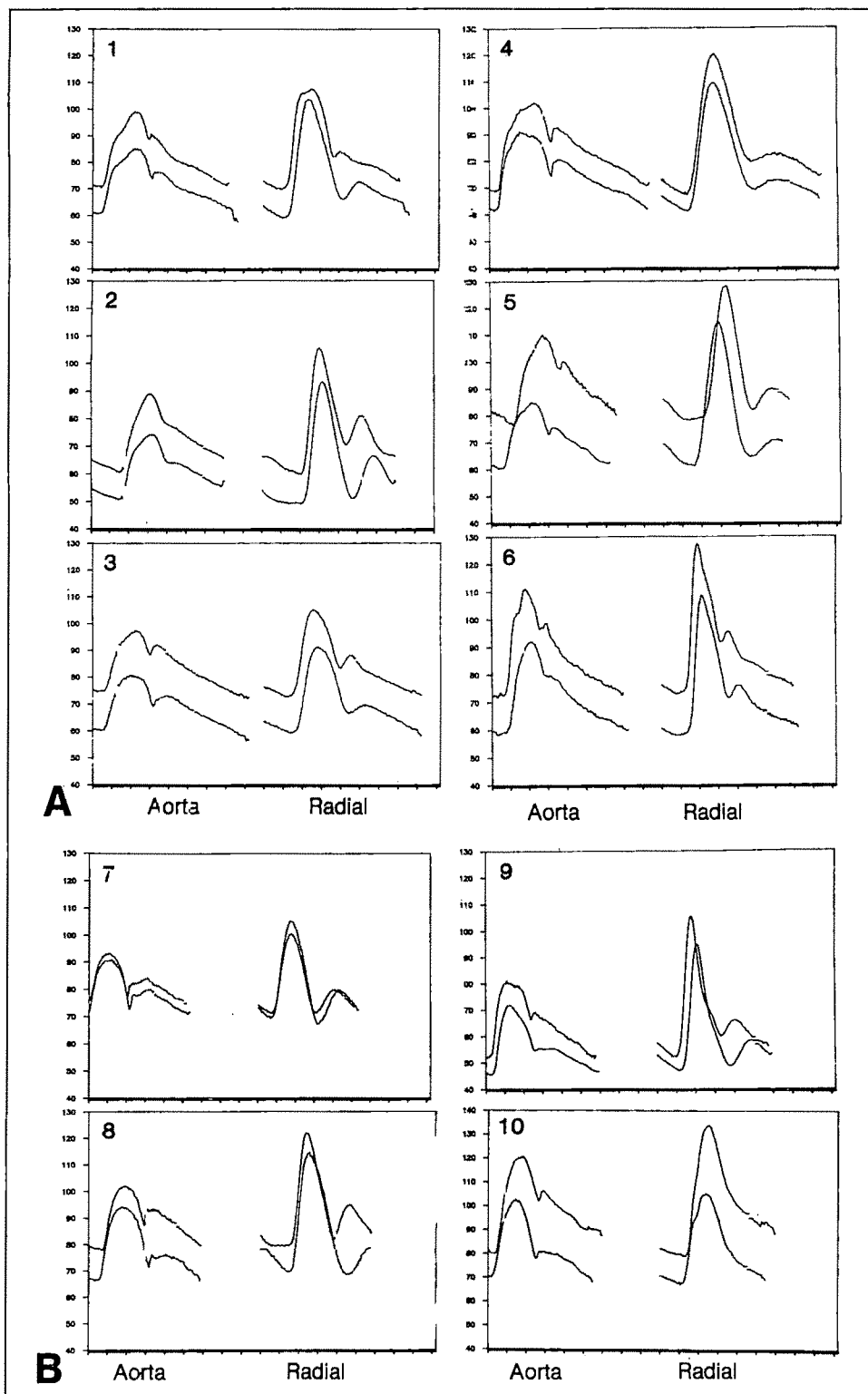


FIGURE 1. Averaged aortic and radial arterial pressure recordings before and during nitroprusside infusion in 10 patients with severe cardiac failure. Each pressure pulse is the average of 10 successive beats. **A**, group I shows a late systolic increase in aortic pressure drug control recordings. **B**, in group II no late systolic aortic pressure peak is apparent during control recordings.

ments of pulmonary artery, pulmonary capillary wedge, aortic and radial pressures and cardiac output were recorded 5 minutes after commencing the maximal dose of nitroprusside.

Analysis: The pressure signals recorded on electromagnetic tape were digitized at a frequency of 200 Hz. At least 20 consecutive beats were used for the analysis. Peak systolic, diastolic and mean aortic and radial arterial pressures were calculated automatically by the analysis program. Mean pressures were calculated by numerical integration of the pressure curves. Left ventricular ejection time was measured as the time interval between the onset of the aortic pressure upstroke and the nadir of the diastolic notch. Pulse transmission time was measured as the time difference between the onset of the aortic and radial pressure waves.

Statistics: The results are expressed as mean \pm standard error of the mean. Data were compared by paired 2-tailed *t* test. *P* < 0.05 was considered statistically significant.

RESULTS

Left ventricular performance was reduced in all 10 patients as evidenced by a cardiac index of 1.80 ± 0.1 liters/min/m² and an elevated pulmonary capillary wedge pressure of 25 ± 4 mm Hg. Nitroprusside resulted in an improvement of cardiac index to 2.6 ± 0.3 liters/min/m² (*p* < 0.001), a decrease in systemic vascular resistance (control $1,989 \pm 117$ dynes s cm⁻⁵, nitroprusside $1,159 \pm 62$ dynes s cm⁻⁵) and a decrease in pulmonary capillary wedge pressure to 18 ± 2 mm Hg (*p* < 0.001). Peak radial artery systolic pressure was an average of 15 ± 2 mm Hg above aortic systolic pressure (aortic systolic 98 ± 3 mm Hg, radial 113 ± 4 mm Hg) whereas there was no significant difference between either aortic and radial arterial diastolic or mean pressures. Nitroprusside reduced mean aortic pressure from 80 ± 3 to 69 ± 2 mm Hg, yet there was no significant change in heart rate (88 ± 3 to 87 ± 3 beats/min). Aortic systolic pressure was reduced from 98 ± 3 to 85 ± 3 mm Hg, whereas radial pressure decreased from 113 ± 4 to 104 ± 3 mm Hg. The augmentation of systolic pressure from ascending aorta to radial artery increased after nitroprusside from 15 ± 2 to 19 ± 2 mm Hg (*p* < 0.05). Left ventricular ejection time was increased by nitroprusside from 220 ± 8 to 234 ± 9 ms (*p* < 0.001) and transmission time of the arterial pulse from ascending aorta to radial artery increased from 99 ± 4 to 113 ± 3 ms (*p* < 0.01), indicating a reduction in arterial pulse wave velocity.

The aortic and radial arterial pressures before and during nitroprusside infusion are shown in Figure 1. In 6 subjects (1 through 6) (Figure 1A) the aortic peak systolic pressure results from a late systolic pressure peak (group I), whereas in subjects 7 through 10 (Figure 1B) no such late pressure peak is identifiable (group II).

Group II patients had more rapid heart rates (96 ± 4 beats/min) compared to group I (78 ± 2 , *p* < 0.05), yet cardiac index, mean aortic pressure and left ventricular ejection times were not significantly different. Aor-

tic systolic pressure decreased in group I patients from 102 ± 8 to 86 ± 6 mm Hg while radial artery systolic pressure decreased from 115 ± 9 to 106 ± 9 mm Hg. In group II aortic pressure decreased from 91 ± 11 to 84 ± 9 mm Hg and radial pressure from 109 ± 8 to 102 ± 9 mm Hg. The systolic pressure augmentation between aortic and radial artery was increased during nitroprusside infusion in the group I patients (control 13 ± 4 mm Hg, nitroprusside 20 ± 6 mm Hg, *p* < 0.025) yet group II patients were unchanged (control 18 ± 6 , nitroprusside 18 ± 7 mm Hg). In group I, nitroprusside reduced the amplitude of the late systolic aortic pressure wave in 5 of 6 of the subjects (Figure 1A). Although the amplitude of the late systolic aortic pressure wave could not be quantified in most patients, its reduction by nitroprusside is sufficient in magnitude to explain the relatively lower aortic systolic pressure and thus the increased aortic to radial arterial pressure augmentation.

Although nitroprusside increased left ventricular ejection time from 220 ± 8 to 234 ± 9 ms (*p* < 0.005), there was no relation between the change in left ventricular ejection time and the augmentation of systolic pressure between the aorta and radial arteries in either of the 2 groups. In addition, the increase in pulse transmission time between ascending aorta and the radial artery did not correlate with the augmentation of systolic pressure.

DISCUSSION

This study shows that nitroprusside may reduce aortic systolic more than radial arterial systolic pressure. As a consequence radial arterial systolic pressure cannot be used as a reliable indicator of the effect of a vasodilator on the pressure load imposed by the arterial system on the failing left ventricle. Nitroprusside resulted in beneficial hemodynamic changes in this group of patients with severe cardiac failure. Cardiac output increased and left ventricular filling pressures were reduced in association with a decrease in aortic pressure. In some patients, however, nitroprusside reduced aortic systolic pressure more than is apparent from the decrease of radial arterial pressure. These patients (group I) had an identifiable aortic late systolic pressure peak that was reduced by nitroprusside.

The late systolic aortic pressure peak results from reflections returning to the ascending aorta from the lower body.³ The same reflections are observed later in the upper limb vasculature as a delayed secondary wave.² Nitroprusside reduced the amplitude of this aortic late systolic peak and altered the contour of the radial arterial pressure wave, changes that imply a reduction or delay of reflections.³ Previous studies have shown that nitroprusside not only reduces arteriolar resistance and increases arterial compliance, but also both delays and decreases wave reflections in the ascending aorta.⁴ Nitroglycerin also reduces the amplitude of the late systolic aortic pressure peak⁵ due to a reduction of reflections.^{6,7} Kelly et al⁸ recently showed that nitroglycerin reduces the aortic late systolic pressure peak with little change in brachial systolic pressure in subjects with good ventricular function. Thus, it is likely

that the present findings are also applicable to patients who are not in cardiac failure. The same investigators⁹ also showed that the vasodilating β -adrenergic agent dilevalol exerts a similar differential effect on arterial systolic pressures in central and peripheral arteries, whereas nonvasodilating β blockade with atenolol causes no differential reduction of central arterial systolic pressures. Thus, other vasodilator agents that change wave reflection may reduce central arterial systolic pressure more than is evident from any change in peripheral arterial pressure.

Limitations: Without simultaneous measurement of aortic input impedance it is not possible to be certain that the lower aortic late systolic pressure was due to reduced reflections, as changes in the aortic flow wave contour or duration may result in important alterations of the pressure contour. Yet in the present study left ventricular ejection was prolonged by nitroprusside, an effect that might be expected to increase rather than decrease the late systolic aortic pressure peak.¹⁰

The aortic pressure measured using a high fidelity micromanometer catheter was compared with pressures recorded from a fluid-filled system in the radial artery. Although fluid-filled transducers are a potential source of artifactual pressure recordings, differences between the systems were minimized by ensuring that the fluid-filled system had an adequate frequency response.

Clinical implications: Many clinical and investigational assessments of ventricular performance are based on estimates of central aortic pressure, sometimes calibrated from measurements of peripheral arterial pres-

sure.¹¹ Because peripheral and aortic systolic pressures are not reduced equally by nitroprusside, the results of the present study question the validity of peripheral pressure measurements for the assessment of left ventricular afterload and suggest that they must be used with great caution, especially when using maneuvers that cause vasodilatation.

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Early and Late Changes in Left Ventricular Systolic Performance After Percutaneous Aortic Balloon Valvuloplasty

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To evaluate early and late hemodynamics after aortic valvuloplasty, 17 patients underwent first-pass radionuclide angiocardiology with simultaneous high-fidelity micromanometer pressure before, 10 minutes after and 6 months after aortic valvuloplasty. Pressure-volume and stress data were assessed. Immediately after the procedure, no significant change was observed in heart rate, systemic blood pressure, cardiac output or aortic insufficiency (as measured by visual or quantitative aortography). The mean and peak transvalvular gradient decreased from 64 to 36 mm Hg ($p < 0.001$) and 76 to 38 mm Hg ($p < 0.001$), respectively. The mean aortic valve area increased from 0.5 to 0.8 cm² ($p < 0.001$). Using echocardiography, meridional end-systolic wall stress decreased from 81 to 63 · 10³ dynes/cm² ($p < 0.001$). Left ventricular ejection fraction increased from 0.48 to 0.54 ($p < 0.01$), end-diastolic volume decreased from 161 to 143 ml ($p < 0.001$) and end-diastolic pressure decreased from 18 to 13 mm Hg ($p < 0.01$). Left ventricular stroke work (the area of the pressure-volume loop) also decreased from 17.5 to 14.7 · 10⁶ ergs ($p < 0.001$). The loop shifted to the left and downward. At the 6-month study, the mean and peak aortic valve gradient increased from 36 to 56 mm Hg ($p < 0.001$) and 38 to 61 mm Hg ($p < 0.001$), respectively. The aortic valve area worsened (0.8 to 0.5 cm², $p < 0.001$), end-systolic wall stress increased (63 to 84 · 10³ dynes/cm², $p < 0.001$) and the left ventricular ejection fraction decreased (0.54 to 0.49; $p < 0.02$). The end-diastolic volume increased (143 to 159 ml) along with the end-diastolic pressure (13 to 21 mm Hg, $p < 0.01$). Left ventricular stroke work (14.7 to 16.3 · 10⁶ ergs) was not different from baseline. The loop returned toward baseline. The changes seen in ejection fraction, however, were primarily related to changes in loading conditions. At 6 months, restenosis occurred in most patients, but was not always accompanied by a worsening of clinical status. The pressure-volume loop shifted back toward baseline and the ejection fraction decreased as end-systolic stress increased. There were little data to support an intrinsic change in myocardial contractile performance at any postprocedural interval

after aortic valvuloplasty. Rather, the changes in ejection dynamics appeared primarily to be a function of altered loading conditions.

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Chronic left ventricular outflow obstruction from valvular aortic stenosis evokes compensatory left ventricular geometric remodeling in order to minimize wall stress and maintain the cardiac output. Percutaneous balloon aortic valvuloplasty has been applied as a therapeutic option for patients at high surgical risk with severe aortic stenosis.¹⁻³ The short-term changes seen after the procedure are complex, and it is unclear whether changes in loading conditions, inotropy or both affect the results obtained. This investigation records left ventricular pressure and volume data in patients immediately before and both early and late after percutaneous balloon aortic valvuloplasty to characterize the serial changes in left ventricular systolic performance that occur immediately after the procedure and at 6-month recatheterization. The use of radionuclide angiography simultaneously with high-fidelity pressure data allowed for characterization of pressure-volume relations without perturbation of the hemodynamics.

METHODS

Population: After obtaining approval from the Duke University Institutional Review Board, 17 consecutive patients with degenerative, calcific tricuspid aortic stenosis (defined by both echocardiographic and angiographic assessment) were entered into the study. Informed consent was obtained from all patients. There were 5 men and 12 women with a mean age of 70 ± 19 years. Eleven patients presented with Canadian Heart Association angina class III or IV, 13 patients with New York Heart Association congestive heart failure class III or IV and 3 patients with syncope or presyncope. In addition, 9 patients had significant (at least 1 artery with luminal diameter narrowing ≥75%) coro-

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TABLE I Angiographic and Hemodynamic Data

Patient	Age	CAD	AI 1	AI 2	AI 3	HR 1 (beats/min)	HR 2 (beats/min)	HR 3 (beats/min)	AO 1 (mm Hg)	AO 2 (mm Hg)	AO 3 (mm Hg)	Fick 1 (liters/min)	Fick 2 (liters/min)	Fick 3 (liters/min)	GRAD 1 (mm Hg)	GRAD 2 (mm Hg)	GRAD 3 (mm Hg)	AVA 1 (cm ²)	AVA 2 (cm ²)	AVA 3 (cm ²)	EDP 1 (mm Hg)	EDP 2 (mm Hg)	EDP 3 (mm Hg)
1	76	2	1	1	1	64	60	67	95	85	95	4.4	6.1	3.1	81	70	67	0.4	0.7	0.3	9	5	30
2	80	0	1	1	1	72	72	91	95	90	130	4.3	3.5	3.4	75	27	62	0.3	0.9	0.4	14	10	12
3	01	1	1	1	1	82	90	78	86	77	77	4.1	4.6	1.9	37	28	36	0.5	0.7	0.3	16	19	40
4	82	2	2	2	2	91	91	88	90	85	53	5.3	4.5	4	86	39	50	0.5	0.7	0.4	18	10	12
5	65	1	2	2	2	85	75	72	85	85	83	6.2	6.3	4.8	43	30	46	0.8	1.1	0.7	10	8	12
6	77	0	1	1	1	72	78	72	95	100	83	3.9	3.8	3.1	62	33	57	0.5	0.7	0.4	20	15	25
7	86	3	1	1	1	79	79	54	110	110	133	4.4	2.7	3.4	77	38	62	0.4	0.5	0.4	14	5	20
8	77	0	1	1	1	86	90	73	84	108	103	4.0	4.0	4	69	39	56	0.4	0.5	0.4	34	28	20
9	63	0	2	2	2	87	87	70	88	80	73	5.7	5.1	5.2	47	28	46	0.7	0.9	0.8	20	10	14
10	73	0	2	2	1	70	72	64	95	65	125	3.2	3.2	6	79	53	72	0.3	0.5	0.6	13	10	29
11	83	1	2	2	2	75	73	85	93	81	110	4.8	4.8	5.2	51	27	61	0.6	1.0	0.6	10	12	10
12	81	0	1	1	1	62	67	68	85	97	108	4.1	3.9	4.7	58	33	45	0.5	0.8	0.8	12	15	15
13	57	0	1	1	1	76	61	67	65	77	102	5.8	4.8	5.4	106	45	65	0.5	0.8	0.5	32	25	21
14	67	3	1	1	1	85	86	88	103	114	91	4.5	4.2	5.3	47	23	50	0.6	0.9	0.7	10	10	16
15	76	1	1	1	1	60	56	55	108	103	92	3.7	3.7	3.2	62	41	58	0.5	0.6	0.4	15	15	18
16	72	0	2	2	2	61	55	51	95	110	105	3.4	3.3	4.9	93	48	77	0.3	0.6	0.6	35	20	40
17	66	0	2	1	2	96	90	104	70	88	83	3.5	3.4	4.1	22	16	20	0.7	1.0	0.7	21	10	20

Serial hemodynamic data are presented for the population with measurements before (1), 10 minutes after (2) and 6 months after (3) valvuloplasty. AI = angiographic aortic insufficiency; AO = mean aortic root pressure; AVA = aortic valve area; CAD = coronary artery disease; EDP = end-diastolic pressure; Fick = Fick cardiac output; GRAD = mean aortic valve gradient; HR = heart rate.

nary artery disease (Table I). Patients were asked to return for a routine 6-month invasive evaluation. At the 6-month follow-up, 9 patients were considered "asymptomatic" (New York Heart Association class I or II) and 8 were considered symptomatic (New York Heart Association class III or IV) for congestive heart failure.

Experimental design: CARDIAC CATHETERIZATION AND ANGIOGRAPHY: All catheterizations were performed using the femoral approach. Right heart pressures were measured with a fluid-filled catheter. A temporary pacemaker was positioned before the procedure. Non-ionic contrast was used for coronary angiography, aortography and left ventriculography in all patients. After the procedure, hemodynamic data, aortography and ventriculography were repeated. Oxygen consumption for the calculation of Fick cardiac output was accomplished with Sensormedic MMC Horizon System. The aortic valve area was determined by use of the Gorlin formula.

Simultaneous left ventricular and aortic pressures were measured with a high-fidelity, dual-sensor micromanometer catheter (Millar Instruments, Inc.) inserted through a number 14Fr UMI (Universal Medical Instrument Corp.) sheath in the right or left femoral artery. Micromanometer catheters were balanced externally and calibrated to the fluid-filled lumen pressures after insertion. A Hewlett-Packard 8086A computerized pressure recorder transferred data to a Gould 1000-C electrostatic strip chart. Digital left ventricular pressure data were also acquired simultaneously with radionuclide image data using the Scinticor multicrystal gamma camera (Scinticor Inc.).

Aortic regurgitation was visually graded on a scale from 0 to 4+ using standard criteria. Aortic regurgitation was also quantitatively assessed using a fixed, pre-selected region of interest in the aorta and left ventricle. The ratio of aortic to left ventricular videodensity at maximum aortic contrast density was recorded and represented a quantitative measure of aortic regurgitation. This method was suggested by Klein et al⁴ and has been previously used by this laboratory to assess aortic regurgitation severity after aortic valvuloplasty.⁵

VALVULOPLASTY PROCEDURE: A single 20 mm 5.5 cm Mansfield (Boston Scientific) aortic valvuloplasty balloon was percutaneously inserted through the right or left femoral artery in all patients. A minimum of three 10 to 60-second dilations were accomplished in all cases. There were no significant acute complications.

SIX-MONTH RECATETERIZATION: The 6-month cardiac catheterization was undertaken using the same protocol as mentioned before with duplication of all radiographic angles and careful reproduction of all high-fidelity pressure and oximetric methods.

RADIONUCLIDE ANGIOCARDIOGRAPHY: Initial transit radionuclide angiocardiograms were acquired at 20-ms intervals using the Scinticor multicrystal gamma camera. Ten mCi of technetium-99m diethyltriaminepentacetic acid was injected as a bolus through a 20-gauge right external jugular venous Teflon catheter with a data acquisition time of 25 seconds for each study. Proprietary

software was used to calculate cardiac output, pulmonary blood volume, left and right ventricular ejection fraction, left ventricular end-diastolic volume, end-systolic volume and peak ejection rate. Volumetric measures used area-length assumptions. The accuracy and reproducibility of these measurements have been reported in previous investigations.⁶⁻⁷ The high-fidelity left ventricular pressure data were matched to each 20-ms frame of radionuclide image data, allowing construction pressure-volume loops from an average cardiac cycle.⁸

END-SYSTOLIC MIDWALL MERIDIONAL WALL STRESS: M-mode and 2-dimensional echocardiograms were obtained using a Hewlett-Packard echocardiograph before, 1 hour after, and 6 months after the valvuloplasty procedure to estimate left ventricular end-systolic dimension and end-systolic wall thickness in the short-axis projection. If wall motion abnormalities were present, only the normally contracting wall segment was used because the formula assumes uniform contraction. Of the 9 patients with coronary disease, 2 patients had posterior wall motion abnormalities angiographically and 1 patient had septal wall motion abnormalities that could have affected the results. In no patient were abnormalities of both septal and posterior wall present. Left ventricular end-systolic (ES) midwall meridional wall stress (10^3 dyne/cm²) was calculated using the following formula⁹:

$$\frac{0.334 \times (\text{echocardiographic ES dimension}) \times \text{ES pressure}}{1 + \text{ES wall thickness/ES dimension}}$$

STATISTICAL ANALYSIS: The observed changes before and after valvuloplasty were analyzed for statistical significance ($p < 0.05$) using the Student's paired t test and the Wilcoxon signed rank test. In order to compare hemodynamic and volumetric data between patients who

were doing well at 6-month follow-up ($n = 9$) with those who were symptomatic ($n = 8$), the Student's unpaired t test and the Wilcoxon rank sum test were also used.

RESULTS

No statistically significant change was recorded for the population at any time during the study in regard to heart rate, Fick cardiac output, radionuclide cardiac output or mean aortic root pressure (Table I). This allowed data at the 3 time periods to be analyzed on a beat-to-beat basis. Additionally, no change was noted in right atrial pressure (5 ± 2 to 7 ± 4 to 9 ± 6 mm Hg), pulmonary artery diastolic pressure (28 ± 9 to 26 ± 11 to 28 ± 10 mm Hg) or pulmonary capillary wedge pressure (18 ± 6 to 16 ± 8 to 18 ± 6 mm Hg). Seven of 17 patients required 1 unit of packed red blood cells to be transfused after the procedure. Intravenous crystalloid was given (0.5 liters) to all patients in order to maintain stable pulmonary artery diastolic pressure during the procedure. No patient needed transfusion at recatheterization.

The degree of aortic regurgitation did not vary significantly during the study period by either visual methods or quantitative assessment. Quantitatively, the mean ratio of aortic to left ventricular videodensity at maximal aortic contrast density was 0.37 before, 0.38 immediately after valvuloplasty and 0.41 at 6 months.

Early after valvuloplasty, left ventricular systolic pressure decreased (217 ± 42 to 183 ± 29 mm Hg; $p < 0.001$), peak-to-peak aortic valve gradient decreased (76 ± 28 to 38 ± 16 mm Hg; $p < 0.001$), mean aortic valve gradient decreased (64 ± 21 to 36 ± 13 mm Hg; $p < 0.001$) and the aortic valve area increased from 0.51 ± 0.14 to 0.76 ± 0.10 cm² ($p < 0.001$) (Table I). Left

FIGURE 1. Pressure-volume data is shown from a representative patient (number 2 in Tables I and II) before, 10 minutes after and 6 months after valvuloplasty.

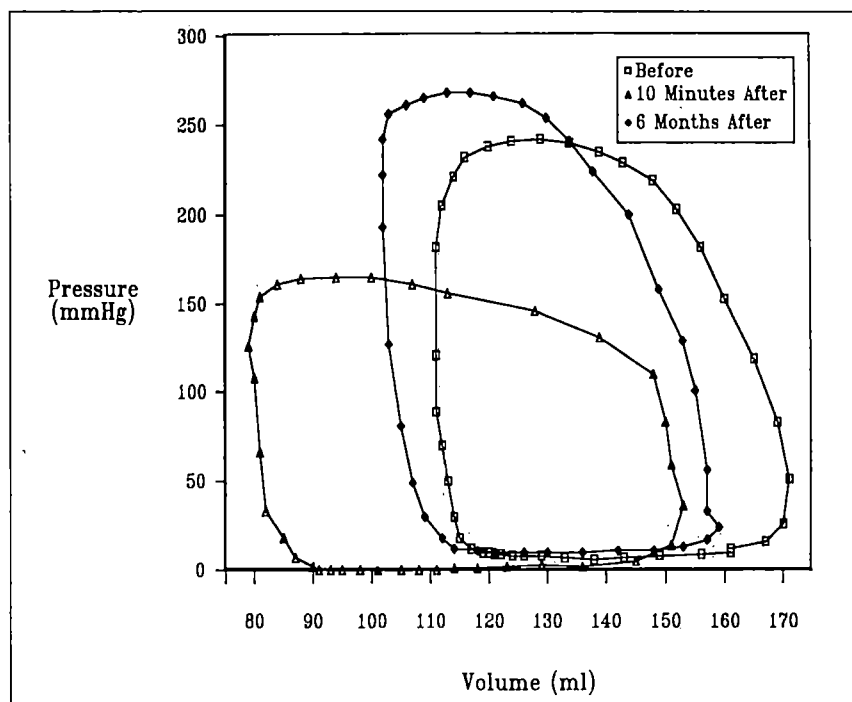


TABLE II Radionuclide and Echocardiographic Data

Patient	rnCO 1 (liters/min)	rnCO 2	rnCO 3	LVEF 1 (%)	LVEF 2	LVEF 3	EDV 1 (ml)	EDV 2	EDV 3	SW 1 (10 ⁶ ergs)	SW 2	SW 3	WS 1 10 ³ dynes/cm	WS 2	WS 3	PER 1 (ml/s)	PER 2	PER 3
1	4.7	4.5	4.8	55	61	56	133	122	128	18.5	8.2	17.4	151	97	174	243	240	240
2	3.6	4.1	5.0	31	40	37	160	141	149	13.3	10.0	15.3	130	73	115	208	417	206
3	4.0	3.7	3.7	24	25	21	203	166	225	8.3	9.7	8.8	116	112	121	255	194	180
4	7.4	7.5	8.2	59	69	56	138	119	167	22.6	18.5	20.5	121	97	128	346	398	449
5	8.8	8.1	8.7	66	79	69	157	137	176	26.8	21.8	21.4	29	24	30	477	594	511
6	5.7	6.4	6.0	52	60	48	153	137	175	18.6	18.0	17.2	125	97	107	320	341	354
7	6.0	6.5	5.3	53	68	60	144	121	163	21.1	17.4	28.5	31	17	62	251	370	316
8	6.8	4.3	4.1	39	43	57	203	164	99	8.8	8.8	12.4	113	84	104	191	281	161
9	4.7	4.4	4.9	35	36	38	154	139	183	10.3	9.4	12.5	130	99	115	262	276	279
10	7.9	7.4	6.2	75	69	50	150	149	194	28.8	25.3	23.4	46	38	71	NA	NA	NA
11	5.7	5.9	6.2	39	43	48	194	189	152	17.5	14.1	17.3	NA	NA	NA	319	341	323
12	5.3	6.3	6.2	57	70	68	151	135	135	19.9	17.3	22.6	30	24	22	370	478	482
13	6.4	4.6	3.7	60	68	67	141	111	82	20.8	15.8	12.6	31	28	38	301	269	208
14	4.5	5.1	4.3	43	53	37	122	111	132	14.4	12.6	8.0	37	34	31	NA	NA	NA
15	4.1	3.9	3.3	54	60	46	125	115	129	15.0	11.9	11.5	101	87	106	299	238	212
16	7.3	6.8	5.7	59	66	64	202	188	174	29.3	27.3	27.2	39	33	41	223	495	388
17	2.6	2.5	3.1	13	15	12	211	188	245	3.5	4.3	4.0	59	58	71	113	185	110

Serial radionuclide data are listed for the population before (1), 10 minutes after (2) and 6 months after (3) valvuloplasty.

* 1 hour after procedure.

EDV = end-diastolic volume; LVEF = left ventricular ejection fraction; NA = not available; PER = peak left ventricular ejection rate; rnCO = radionuclide angiography cardiac output; SW = stroke work. WS = end-systolic meridional wall stress.

ventricular ejection fraction increased (0.48 ± 0.16 to 0.54 ± 0.18 ; $p < 0.001$), peak left ventricular ejection rate increased (-291 ± 91 to -341 ± 118 ml/s; $p < 0.05$), left ventricular end-systolic volume decreased from 161 ± 29 to 143 ± 27 ml ($p < 0.001$), end-systolic volume decreased (87 ± 39 to 68 ± 36 ml; $p < 0.001$) and end-diastolic pressure decreased from 17 ± 8 to 13 ± 6 mm Hg ($p < 0.01$, Table II). Left ventricular stroke work decreased short-term after valvuloplasty from 17.5 ± 7.3 to 14.7 ± 7.1 10^6 ergs ($p < 0.001$, Figure 1). The peak positive first derivative of the left ventricular pressure decreased slightly ($1,616 \pm 420$ to $1,465 \pm 220$ mm Hg/s) and end-systolic pressure-volume ratio did not change (2.9 ± 1.3 to 3.2 ± 1.6 mm Hg/ml). Therefore, early after valvuloplasty, there was a significant decrease in the amount of aortic outflow obstruction.

For 16 patients with an adequate echocardiographic end-systolic image, calculated meridional end-systolic wall stress also decreased from 81 ± 45 to 62 ± 34 10^3 dynes/cm² ($p < 0.001$, Table II).

Six months after valvuloplasty, left ventricular systolic pressure had increased from 183 ± 29 to 223 ± 42 mm Hg ($p < 0.001$), peak-to-peak aortic valve gradient increased from 33 ± 16 to 61 ± 13 mm Hg ($p < 0.001$), mean aortic valve gradient increased from 36 ± 12 to 56 ± 13 mm Hg ($p < 0.001$) and aortic valve area decreased from 0.76 ± 0.19 to 0.53 ± 0.17 cm² ($p < 0.001$, Table I). Left ventricular ejection fraction decreased from 0.54 ± 0.18 to 0.49 ± 0.16 ($p < 0.001$), peak left ventricular ejection rate decreased from -341 ± 118 to -249 ± 122 ml/s ($p < 0.02$), left ventricular end-diastolic volume increased from 143 ± 27 to 159 ± 41 ml ($p < 0.07$), end-diastolic pressure increased from 13 ± 6 to 21 ± 10 mm Hg ($p < 0.01$) and end-systolic volume increased from 68 ± 36 to 85 ± 47 ml ($p < 0.05$, Table II). Left ventricular stroke work also increased, compared to the short-term value from 14.7 ± 7.1 to 16.3 ± 7.1 10^6 ergs (Figure 1). The peak positive first

derivative of the left ventricular pressure increased slightly from $1,465 \pm 220$ to $1,737 \pm 457$ mm Hg/s and end-systolic pressure-volume ratio did not change (3.2 ± 1.6 to 3.1 ± 1.7 mm Hg/ml). Meridional end-systolic wall stress ($n = 16$) increased from 62 ± 34 to 84 ± 44 10^3 dynes/cm² ($p < 0.001$, Table II). No change was observed in echocardiographically determined systolic wall thickness at the 3 study intervals (1.94 ± 0.49 vs 1.93 ± 0.49 vs 1.82 ± 0.43 cm). Electrocardiographic evidence of left ventricular hypertrophy was noted in 14 patients with 3 other patients exhibiting left bundle branch block.

No statistically significant difference was found between symptomatic (New York Heart Association class III or IV) and asymptomatic (New York Heart Association class I or II) patient groups 6 months after valvuloplasty for any hemodynamic or radionuclide variable using either the Student's unpaired *t* test or the Wilcoxon rank sum test. When each hemodynamic and volumetric measurement at 6 months was compared to the value obtained before valvuloplasty, no significant change was observed in any variables, except the mean and peak-to-peak aortic valve gradients were numerically less at 6 months ($p < 0.01$).

DISCUSSION

In patients with chronic aortic stenosis, left ventricular function adapts to overcome the outflow obstruction by elevating left ventricular pressure. This increase in pressure results in hypertrophy that decreases wall stress. Symptoms of congestive heart failure occur when myocardial hypertrophy and other compensatory mechanisms are either no longer able to overcome the amount of valvular obstruction present or result in abnormalities in diastolic filling that restrict inflow. Percutaneous balloon aortic valvuloplasty immediately decreases left ventricular outflow obstruction, but the long-term effects of this procedure on left ventricular

function are poorly understood. Acquisition of pressure-volume data before, early and late after valvuloplasty allows for serial analysis of systolic ventricular performance that might help address this question. Therefore, to define the short- and long-term effects of aortic valvuloplasty, we measured hemodynamic and volumetric parameters of left ventricular function in 17 patients before, 10 minutes after and 6 months after percutaneous balloon aortic valvuloplasty.

The use of simultaneous high-fidelity pressure and radionuclide angiography allows for the determination of a variety of systolic performance indexes. Immediately after aortic valvuloplasty, there is a significant decrease in the aortic gradient and an increase in aortic valve area. The changes observed here are similar to those reported by others.^{1-3,10} As shown in Figure 1, there is a short-term shift of the pressure-volume loop to the left and downward. The decrease in the LV systolic pressure results in a concurrent decrease in the LV stroke work as determined from the area of the pressure-volume loop.

Therefore, the improvement seen in the ejection fraction measurement is a complex issue. Ejection fraction is a load-dependent variable and particularly sensitive to alterations in both inotropy and afterload, with preload influences generally of lesser importance.⁹ The decrease in preload observed in this study would tend to decrease any ejection phase index, such as the ejection fraction, while the decreased afterload that results would tend to increase this parameter. Thus, the overall result of loading conditions should probably be to increase the ejection fraction measurement.

In addition, however, acute occlusion of left ventricular outflow during the valvuloplasty procedure can result in potential "stunning" of the myocardium, as has been demonstrated using analysis of diastolic function (particularly tau)¹¹ and by measurements of coronary sinus lactate.¹² Reflex catecholamine release likely occurs from the hypotension created during balloon inflation and this could impact on inotropy in a positive manner.¹³

It can be concluded, therefore, that the change in ejection fraction observed immediately after the procedure is the result of an interplay of all of these factors. Because heart rate and mean aortic pressure are unchanged immediately after valvuloplasty, the effect of catecholamines appears to be less important than other factors. The ability of the left ventricle to maintain stroke volume and cardiac output at a lower preload, despite the possibility of a decrease in the inotropic state due to "stunning," leads to the conclusion that a decrease in left ventricular outflow obstruction and the consequent decreased afterload are the primary reasons the ejection fraction improvement is observed. This decreased afterload is confirmed by observed decreases in the aortic valve gradient, LV systolic pressure and end-systolic wall stress.

Previous data from this laboratory have shown that during the first 3 days after the procedure, the ejection fraction continues to increase despite no change in the

left ventricular end-diastolic volume.¹⁴ A return in the aortic valve gradient measured by Doppler occurs during this time period and appears to be a function of both an increase in stroke volume and remodeling of the aortic valvular architecture. The data from the current study reveal that these beneficial early hemodynamic changes are frequently reversed by 6 months. At 6 months, the pressure-volume loop returns rightward and upward toward the baseline position. The area of the loop (stroke work) increases to where it is now similar to that observed at baseline. Associated with this change, there was a gradual return of the aortic outflow obstruction in 12 of 17 patients.

Symptomatic status appeared unrelated to the return of the aortic valve gradient. It appears that diastolic left ventricular function correlates best with clinical status at 6 months.¹¹ The ejection fraction at 6 months returned to the baseline value, paralleling the increase in end-systolic wall stress.

The left ventricular end-diastolic volume changed in a variable manner at the 6-month interval. When the preload increased, this resulted in an increase in the left ventricular end-diastolic pressure and peak positive dP/dt . The increase in preload allowed for maintenance of stroke volume despite the decrease in global ejection fraction. Thus, cardiac output could be maintained at a similar heart rate as baseline. Measurements of end-systolic pressure/end-systolic volume at 6 months were similar to the baseline and the postvalvuloplasty values, providing further indirect data that there may have been little change in intrinsic myocardial performance. One is left to conclude that the observed hemodynamic alterations at 6 months are primarily a function of altered loading conditions rather than a change in contractile performance.

When patients who had symptoms of congestive heart failure at 6-month follow-up were compared to those in whom symptoms had improved, several interesting findings were evident. No difference between the groups was found for any variable. Restenosis (return of aortic valve area to baseline) was evident in 12 of 17 patients (71%). Restenosis occurred with a similar frequency in both the symptomatic and "asymptomatic" (New York Heart functional class I or II) groups. Although, no statistical difference between these 2 groups could be shown in any of the baseline variables using either univariate or multivariate analysis, the small sample size makes broad general conclusions regarding this similarity unwise. Regardless, restenosis can clearly occur without concurrent changes in clinical status.¹⁵

These data compare favorably with recatheterization data reported by Block et al¹⁶ in a study of 15 patients who had undergone recatheterization and repeat valvuloplasty at 5.5 months after the initial procedure. Restenosis was noted in all patients, with recurrent symptoms in 13.

The results of this study might be affected by changes in aortic regurgitation after the procedure. Aortic regurgitation was both visually and quantitatively assessed at each study interval and no changes in aor-

tic regurgitation were observed. We have previously shown in a series of 50 patients¹⁴ studied short-term that aortic regurgitation is an uncommon event after this procedure. This conclusion appears to be valid at the 6-month interval as well.

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Detection and Assessment of Severity of Tricuspid Regurgitation Using First-Pass Radionuclide Angiography and Comparison with Pulsed Doppler Echocardiography

Kim A. Williams, MD, Patricia E. Walley, and James W. Ryan, MD

Noninvasive detection and semiquantitative assessment of tricuspid regurgitation (TR) were performed using first-pass radionuclide angiography (RNA), by sampling a region of interest over the right atrium for any tracer entering the right atrium during right ventricular systole. The relative amount of tracer entering the right atrium was quantitated and the results were compared with semiquantitative Doppler echocardiographic grading of TR severity. Using the right ventricular time-activity curve to define end-diastolic and end-systolic frames, the right atrial counts for the 2 or 3 cardiac cycles after the peak right ventricular counts were summed. The right atrial "injection fraction" was calculated using the following formula: $[(\text{end-systolic counts} - \text{end-diastolic counts}) / (\text{end-diastolic counts})] \times 100\%$. The right atrial injection fraction was examined in 51 patients who had good quality RNA and Doppler studies. Of 27 patients with no evidence of TR by Doppler, 26 had a negative right atrial injection fraction. All 24 patients with a positive Doppler for TR had a positive right atrial injection fraction. Comparison of right atrial injection fraction grade ranges with semiquantitative grades of TR severity on Doppler revealed identical grades in 21 of the 24, with a single grade difference in the remaining 3 patients. Thus, right atrial time-activity curve quantitation during routine first-pass RNA allows detection and grading of the severity of TR, with results very similar to pulsed Doppler echocardiography. This simple procedure is easily appended to the evaluation of ventricular performance with first-pass RNA.

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Noninvasive assessment of tricuspid regurgitation (TR) has been attempted with several techniques, including phonocardiography,¹ M-mode and 2-dimensional echocardiography with and without intravenous contrast injection,²⁻⁴ pulsed- and continuous-wave Doppler echocardiography⁵⁻⁷ and radionuclide angiography (RNA).⁸⁻¹⁶ First-pass RNA is essentially a scintigraphic indicator dilution technique, which permits regional time-activity curve analysis in adjacent cardiac chambers.¹⁷ Analysis of right atrial time-activity curves should detect systolic regurgitation of tracer from the right ventricle due to TR. The aims of this study were: (1) to apply first-pass RNA right atrial time-activity curve analysis to the detection of TR, and (2) to compare the first-pass TR detection rate and semiquantitative grading with the noninvasive standard, pulsed Doppler echocardiography.

METHODS

Patients: We reviewed the echocardiographic records of 69 patients who underwent first-pass RNA studies between December 1983 and January 1987. Of these, 51 patients were identified to have had (1) pulsed Doppler echocardiographic mapping of the right atrium adequate for the detection of TR and (2) a well-bolused first-pass RNA study in which both the right atrium and right ventricle were identified within the field of view of the gamma camera. Of the 51 subjects, 17 presented with ischemic heart disease, 14 with valvular heart disease, 7 with hypertensive heart disease and 8 with other cardiac disorders; 5 were found to have no evidence of heart disease. There were 26 women and 25 men. The mean age was 51 years (range 17 to 83).

First-pass radionuclide angiography: Patients were positioned in front of a Baird System-77 multicrystal camera in either the upright-anterior or supine-shallow (30°) right anterior oblique position. The first-pass RNA studies were acquired with a bolus injection of 18 to 23 mCi of technetium-99m diethylene triamine pentaacetic acid into an indwelling catheter (16 or 18 gauge) in a right antecubital or external jugular vein. This bolus was flushed rapidly with 15 to 25 cc of normal saline. The frame mode acquisition intervals varied from 0.025 to 0.050 second/frame, depending on the patient's heart rate.

The right heart phase of the tracer bolus was temporally isolated for analysis. Regions of interest were drawn over the right atrium and right ventricle, taking care to avoid the overlapping region of the tricuspid

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valve plane. The right ventricular region of interest was then adjusted using the automated ventricular ejection fraction software program available from the manufacturer. This program located the peaks (diastole) and valleys (systole) in the time-activity curve generated from the original right ventricular region of interest. The summed systolic image was subtracted from the summed diastolic image, and we used the resulting stroke volume image to draw the final automated right ventricular region of interest. The right atrial region could then be modified to insure exclusion of the right ventricle and the adjacent tricuspid valve plane (Figure 1).

The right atrial and ventricular time-activity curves were then generated over these final regions of interest. An additional region of interest over the superior vena cava was drawn to insure the adequacy of the injected bolus. An acceptable bolus was defined as a mean superior vena cava transit time (estimated by full-width at half-maximum) of ≤ 1.5 seconds. The 3 cardiac cycles after the peak right ventricular activity were analyzed, unless the right ventricle cleared rapidly, in which case only 2 cycles were used. An increase in right atrial counts during right ventricular systole implied TR. The

simultaneous right ventricular time-activity curve was used to identify the individual peak-diastolic and end-systolic frames on the right atrial curve. The percentage of systolic increase in right atrial counts, or right atrial "injection fraction," was quantitated by subtracting the summed peak-diastolic frame counts from the summed end-systolic frame counts, and dividing the result by the summed peak-diastolic frame counts, as in the formula: right atrial injection fraction = right atrial counts (at right ventricular end-systole) - right atrial counts (at right ventricular end-diastole) / right atrial counts (at right ventricular end-diastole) $\times 100\%$.

Based on a preliminary analysis, the right atrial injection fraction results were graded in the following manner: absent TR = $\leq 0\%$; minimal TR = 0 to 4.5%; mild TR = 4.6 to 16%; and moderate-to-severe TR = $>16\%$ (Figures 2 to 4).

Pulsed Doppler echocardiography: Pulsed Doppler ultrasonography was performed with 1 of 2 echo-Doppler flowmeters (ATL Mark 600 or HP 77020A) equipped with a 3.5-MHz piezoelectric transducer. Discrete sampling of intracardiac velocities was performed with these units along a 2- to 15-cm ultrasound beam, by electronically range gating the returning ultrasonic reflections. The localized blood flow velocities are detected by Doppler frequency shifts within the sample volume. The Doppler sample volume was targeted within the right atrium using 2-dimensional echocardiographic imaging (Figure 5). Images were acquired from apical and parasternal windows with the patient in a left lateral recumbent position. This sample volume was used to map the intracardiac velocities in the right atrium, first at the tricuspid valve plane. If systolic turbulent flow lasting at least 80% of systole was noted at the valve level, the systolic velocities were then traced to determine the posterior extent of the regurgitant flow within the right atrium (Figure 6). Because of the limited pulse repetition frequency of pulsed Doppler, high velocities within the right atrium will "wrap around" (aliasing), thus appearing as forward (toward the transducer) as well as backward (away from the transducer) flow (Figure 6).

The posterior extent of the regurgitant stream of velocities was measured and graded in the following manner: absent TR = no significant systolic backward flow; minimal TR = systolic turbulence found only within 1 cm of the valve plane; mild TR = systolic turbulence found beyond 1 cm of the valve plane but not extending to the midright atrium; and moderate-to-severe TR = systolic turbulence extending to or beyond the midpoint of the right atrium. The patients were separated into 4 groups based on the severity of these pulsed Doppler TR grades: group I = no Doppler evidence for TR, group II = minimal TR, group III = mild TR and group IV = moderate-to-severe TR.

Statistics: Using pulsed Doppler echocardiography as the standard, we defined the sensitivity of RNA for TR as the number of patients in whom the RNA demonstrated TR divided by the total number of studies positive for TR by Doppler. Specificity of the RNA for TR was defined as the ratio of negative RNA studies to

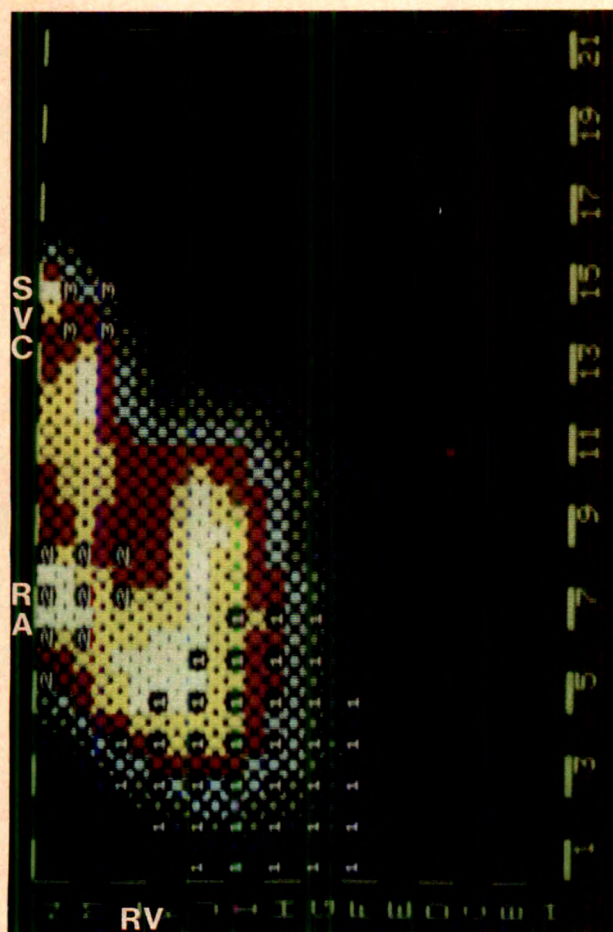


FIGURE 1. Regions of interest over the right ventricle (RV) (1), right atrium (RA) (2) and superior vena cava (SVC) (3) from which time-activity curves were generated. RA and RV regions are drawn to avoid overlap and the tricuspid valve plane.

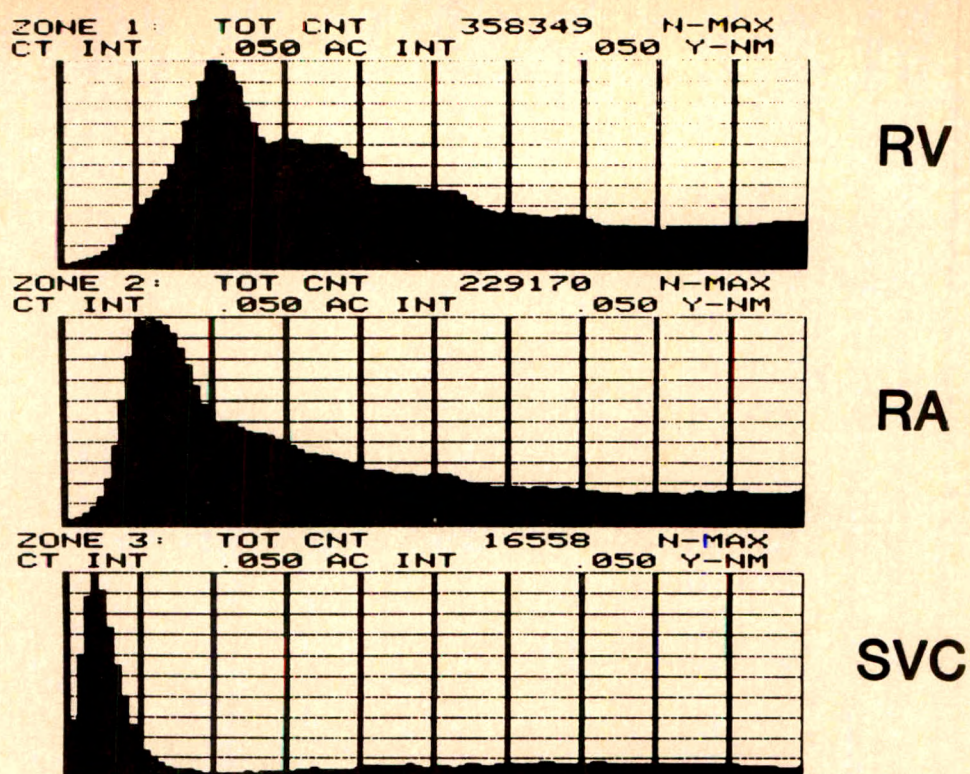


FIGURE 2. Simultaneous RV, RA and SVC time-activity curves in a normal subject with no evidence of tricuspid regurgitation. Note that during RV systole there is no increase in RA counts. Abbreviations as in Figure 1.

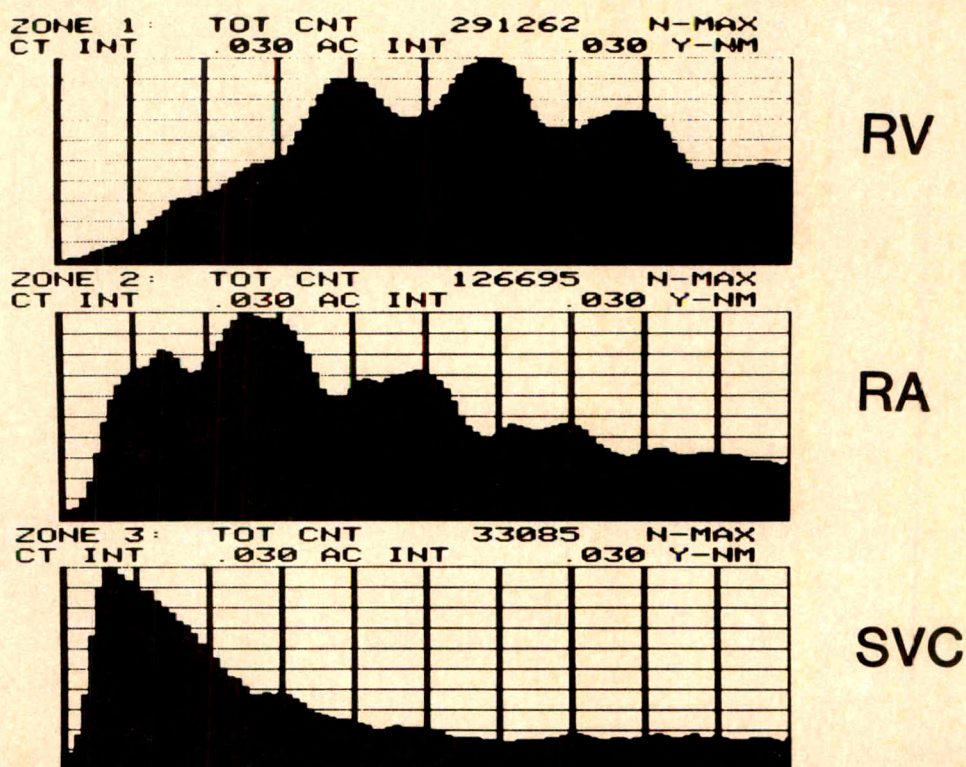


FIGURE 3. Simultaneous RV, RA and SVC time-activity curves in a patient with mild tricuspid regurgitation. Note that during each RV systole after the bolus clears the SVC there is an increase in the RA counts, indicative of tricuspid regurgitation. Abbreviations as in Figure 1.

negative Doppler studies. Patients were separated into 4 groups based on the severity of their pulsed Doppler echocardiographic TR grade. The mean and standard deviation of the right atrial "injection fraction" for each of these groups were compared with its adjacent groups for statistically significant differences using the Student *t* test for the comparison of means.¹⁸ A *p* value <0.05 was considered statistically significant.

RESULTS

Of the total 69 patients, 18 were excluded from the study because of incomplete or poor quality data. RNA bolus transit times were unacceptably prolonged in 2 patients. Inadequate visualization of the right atrium occurred in 5 patients, as the RNA study was primarily intended for left-sided cardiac analysis and the field of view of the multicrystal gamma camera is limited (14 ×

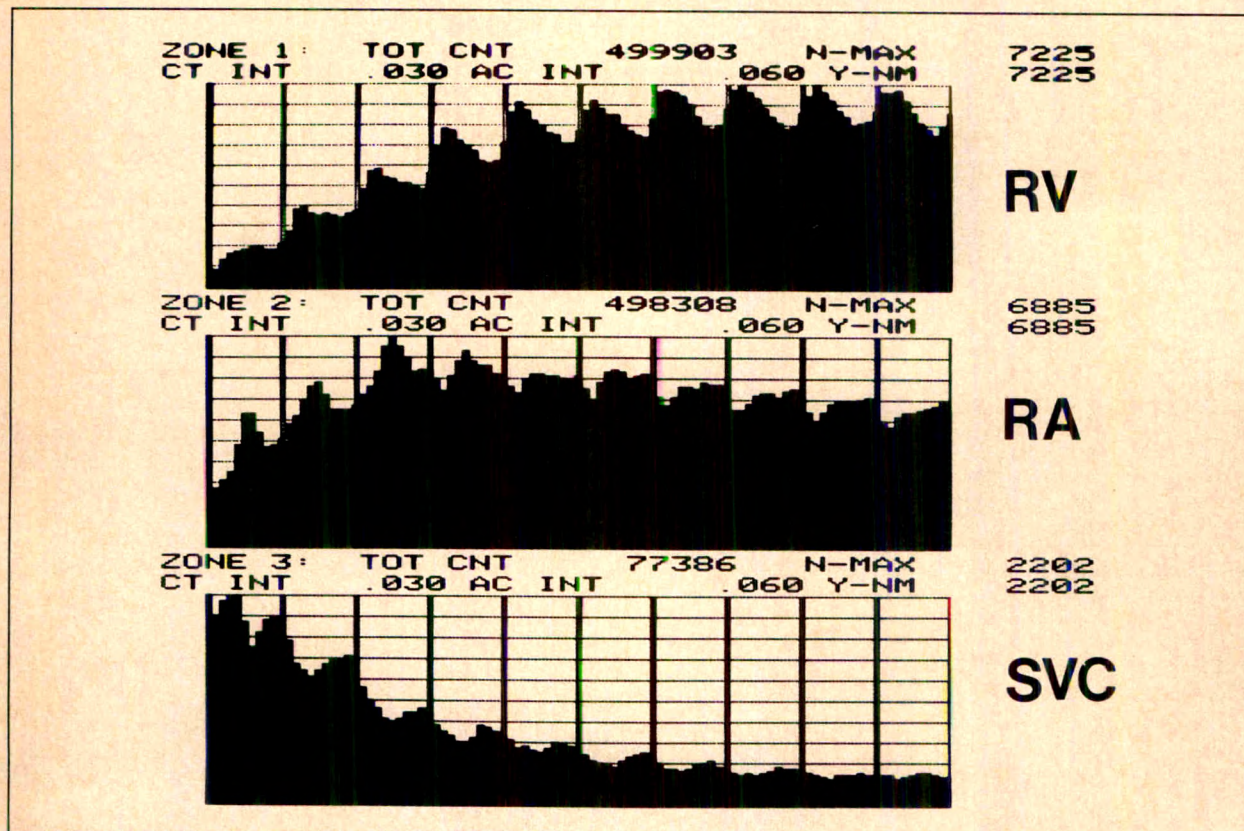


FIGURE 4. Simultaneous RV, RA and SVC time-activity curves in a patient with moderate-to-severe tricuspid regurgitation. Note that during each RV systole after the bolus clears the SVC there is an increase in the RA and SVC counts, indicative of tricuspid regurgitation. Additionally, the transit times through the RA and RV are prolonged. Pulsed Doppler echocardiography in this patient is shown in Figure 6. Abbreviations as in Figure 1.

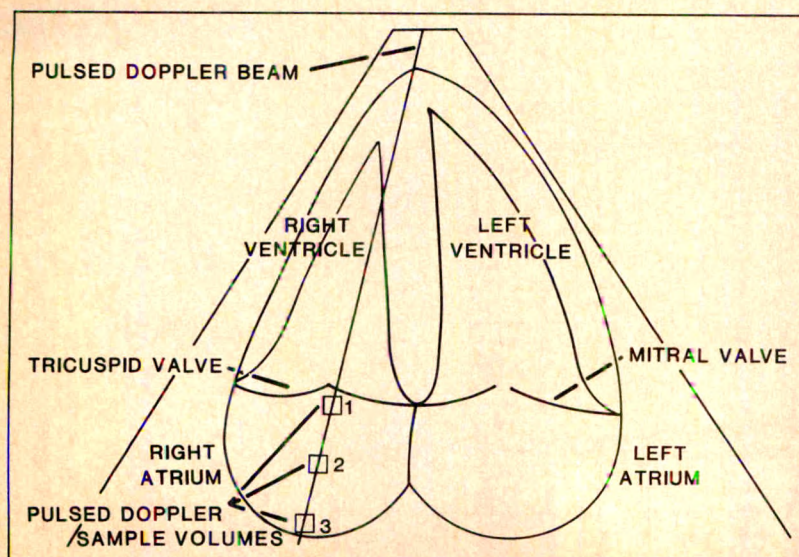


FIGURE 5. Diagram of pulsed Doppler echocardiographic technique, shown from the apical 4-chamber view. A moveable sample volume is electronically localized by range gating of the returning ultrasound reflections. Thus, interrogation and mapping of systolic regurgitant velocities within the right atrium can be performed.

21 cm). There were 11 patients with technically difficult echocardiographic images or right atrial mapping, or both, that were deemed inadequate to define the presence and extent of TR.

Tricuspid regurgitation detection rate: TR was found by either technique in 25 patients. The RNA was positive for TR in only 1 patient with a negative Doppler study. There were no patients with TR that was detected by Doppler that was not detected by RNA. Thus, with Doppler echocardiography as the standard, first-pass RNA demonstrated a sensitivity of 100% and a specificity of 96%.

Tricuspid regurgitation severity grading: The severity of TR by Doppler was used to assess the TR severity grading potential of the RNA right atrial injection fraction quantitation.

There were 27 patients without evidence of TR by Doppler (group I). Of these patients, 26 were negative for TR by RNA, while 1 had mild TR by RNA. The patient with discordant results had echocardiographic diagnoses of tricuspid and mitral valve prolapse. Doppler was performed in the supine position while the RNA was performed sitting upright. With tricuspid prolapse it is possible that TR was present only in the upright position. There were 2 patients in the study with concordant results who also had echocardiographic evidence for both mitral and tricuspid valve prolapse; 1 had mild TR and 1 had no TR by both techniques.

Of the 24 patients with TR by Doppler, 5 were graded as minimal (group II), 13 as mild (group III) and 6 as moderate-to-severe (group IV). Identical TR severity grades on the RNA right atrial injection fraction were found in 21 patients. The remaining 3 patients' TR severity grades differed by only a single grade from the Doppler result, with no discordance in the moderate-to-severe TR group.

For the 27 patients with no Doppler evidence for TR, the mean right atrial injection fraction was $-11.5 \pm 9.9\%$. The 5 patients with minimal TR by Doppler had a mean right atrial injection fraction of $3.9 \pm 1.4\%$. The 13 subjects with mild TR by Doppler had a mean right atrial injection fraction of $7.9 \pm 3.3\%$. In the 6 with moderate-to-severe TR by Doppler the mean right atrial injection fraction was $22.1 \pm 2.3\%$. Statistical comparison of these 4 groups revealed significant distinction of each group by RNA right atrial injection fraction (Table I).

DISCUSSION

Etiology and importance of tricuspid regurgitation:

Tricuspid valvular regurgitation most commonly results from disorders that elevate pulmonary arterial pressure. These include left-sided cardiac failure, pulmonary emboli, primary pulmonary hypertension, chronic obstructive pulmonary disease and congenital heart disease.¹⁹ Tricuspid valve leaflet integrity may be compromised by

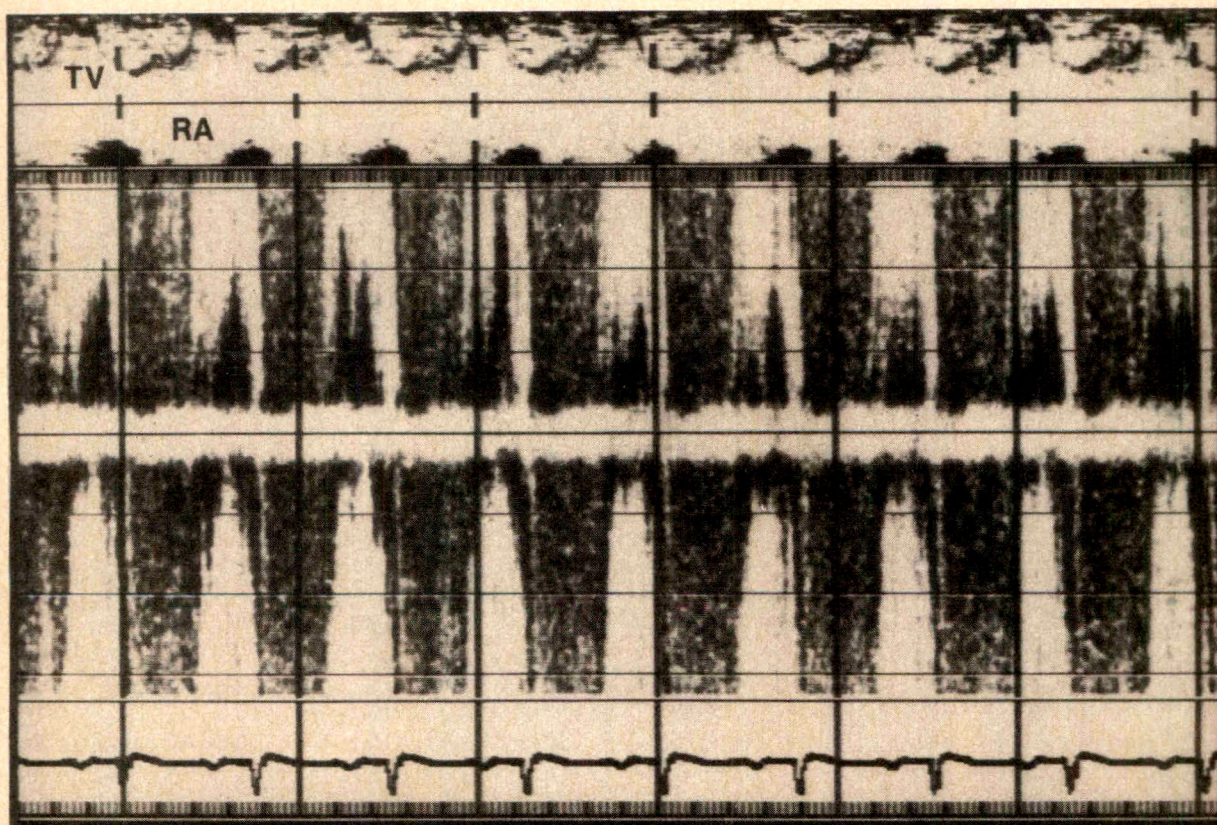


FIGURE 6. Moderate-to-severe tricuspid regurgitation by pulsed Doppler echocardiography. M-mode through the right ventricle, tricuspid valve (TV) and right atrium (RA) are shown at the top. Spectral velocity display in the pulsed mode demonstrates diastolic velocities going toward the transducer (upward), and marked systolic turbulence during systole with high velocities resulting in aliasing of the tricuspid regurgitation signal above and below the zero velocity line.

TABLE I Right Atrial "Injection Fraction" and Doppler Echocardiographic Grading of Tricuspid Regurgitation

Pulsed Doppler Grade	Radionuclide Angiographic RAIF (%)
I (none)	-12 ± 10
II (minimal)	4 ± 1 (p < 0.01 vs I)
III (mild)	8 ± 3 (p < 0.05 vs II)
IV (moderate to severe)	22 ± 2 (p < 0.001 vs III)

Values are mean ± standard deviation.
RAIF = right atrial injection fraction.

trauma, infectious endocarditis, rheumatic fever, infiltrative disorders or metastatic carcinoid tumors. Right ventricular infarction may involve the right ventricular papillary muscles and lead to regurgitation with normal tricuspid leaflets.²⁰

Clinical diagnosis of mild-to-moderate TR may be difficult.²¹ However, unrecognized TR has been found to contribute to surgical morbidity and mortality.²² Noninvasive detection and assessment of the severity of TR has grown in importance, as its surgical management with anuloplasty and medical therapy with vasodilators has developed.²²

Noninvasive assessment of tricuspid regurgitation:

PULSED DOPPLER ECHOCARDIOGRAPHY: Pulsed Doppler echocardiography has become the noninvasive standard for detection of TR in recent years.²² However, accurate estimation of the presence and severity of TR by Doppler is dependent on several factors: (1) the patient's body habitus; (2) ability to obtain an adequate Doppler signal while the ultrasound beam is parallel to the regurgitant flow¹²; and (3) careful interrogation and mapping of the right atrium with the pulsed Doppler sample volume. Radionuclide techniques have the advantage of being less operator and body habitus dependent.

GATED EQUILIBRIUM RADIONUCLIDE ANGIOGRAPHY: Gated equilibrium RNA has been used successfully in the evaluation of left-sided valvular regurgitation.^{16,23-26} Equilibrium RNA has also been recognized to be a useful tool in the diagnosis of isolated tricuspid valvular regurgitation, using a decrease in the left ventricular to right ventricular stroke count ratio,^{14,25,26} or a systolic increase in scintigraphic counts over the liver ("hepatic expansion fraction").^{9,13,15} However, the stroke count ratio method fails to differentiate tricuspid from pulmonary valvular regurgitation, and may be falsely negative in patients with left-sided valvular regurgitation. The analysis of hepatic expansion with gated equilibrium RNA may be more specific for TR than the stroke count ratio method, but has not been studied in subjects with minimal-to-moderate TR, as can be detected with pulsed Doppler echocardiography.

FIRST-PASS RADIONUCLIDE ANGIOGRAPHY: First-pass RNA has also been used to detect TR, using the scintigraphic appearance of tracer in the right atrium, brachiocephalic veins or inferior vena cava during right ventricular systole as an indication of regurgitation.^{10,12}

Time-activity curve analysis of a radionuclide bolus injection was first introduced for the detection of mitral and aortic valvular regurgitation by Metz et al,¹⁷ using a bolus in the pulmonary capillary wedge position in a

canine experimental model. However, right atrial time-activity curve analysis for the diagnosis of TR in patients undergoing routine diagnostic first-pass RNA has not been previously reported.

In our study, we have demonstrated that analysis of the right atrial time-activity curve allows quantitation of the counts that regurgitate across the tricuspid valve, reentering the right atrium during ventricular systole. With any technique for TR, there is difficulty in establishing its true diagnostic accuracy, since an absolute reference standard is lacking. Right ventricular cineangiography has been proposed as the standard for TR by some investigators.²⁷ However, this procedure is invasive and may irritate the right ventricle, causing premature ventricular contractions that result in an inaccurate assessment of TR. This technique also may produce TR because the catheter traverses the tricuspid valve.^{27,28} Using right atrial pulsed Doppler echocardiography as the reference standard, our right atrial time-activity curve analysis revealed a diagnostic sensitivity of 100% and a specificity of 96% in this retrospective study. In addition, there was good correlation between these noninvasive estimates of the relative severity of TR.

Limitations: There are potential technical limitations to both the Doppler and RNA methods for the evaluation of TR, as demonstrated by the need to exclude 19 patients from analysis due to inadequacy of the data. The RNA technique requires careful positioning in front of a high count-rate capable first-pass camera, a relatively large intravenous catheter in a large vein and strict adherence to a bolus-flush technique so that tracer is rapidly delivered to the right atrium. A possible source of error in the RNA technique may occur due to cyclic respiratory variation in the amount of TR (Carvallo's sign), since relatively few beats (2 to 3) are used in the analysis.

Doppler ultrasonography is often technically difficult in the adult cardiology population, especially in barrel-chested or obese individuals with poor ultrasound transmission characteristics. The accurate determination of the extent of TR may be difficult and time consuming. This requires careful right atrial mapping with a small pulsed Doppler sample volume from 1 or more echocardiographic windows. The more recent addition of 2-dimensional color mapping to the pulsed Doppler technique lessens the difficulty of adequate data collection.

A clearer definition of the right atrial injection fraction quantitative separation between minimal and mild grades (groups II and III) with the RNA technique should be possible with additional studies and larger numbers of subjects, although statistical separation of the groups' right atrial injection fractions was possible in this relatively small study.

Clinical implications: This study demonstrates that analysis of the right atrial time-activity curve during routine first-pass RNA is a rapid and easily performed method that can detect and quantitatively grade the severity of TR. In comparison with the current noninvasive standard, pulsed Doppler echocardiography, the RNA technique is both sensitive and specific. Although

pulsed Doppler echocardiography does not require intravenous access, RNA is less frequently technically limited by body habitus. Although further studies of this technique are necessary to help define the role of RNA for the noninvasive diagnosis and management of TR, these data suggest that the accurate assessment of TR may easily be appended to studies of right and left ventricular performance with first-pass RNA.

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Long Follow-Up (to 43 Years) of Ventricular Septal Defect with Audible Aortic Regurgitation

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From 1946 to March 1989, 92 patients (33 women and 59 men) were seen with ventricular septal defect (VSD) and audible aortic regurgitation (AR). The VSD was subcrystal in 62 patients, subpulmonary in 21 and unknown in the remaining 9. The median age of onset of AR was 5.3 years. The risk of developing AR was 2.5 times greater in those with a subpulmonary VSD. The aortic valve was tricuspid in 90% and bicuspid in 10%. Prolapse was seen in 90% of those with subcrystal VSD and in all with subpulmonary VSD. Pulmonary stenosis was seen in 46% of the patients with gradients ranging from 10 to 55 mm Hg. The incidence of infective endocarditis was 15 episodes/1,000 patient years. Among 20 patients followed medically, for 297 patient years, 1 died (1959) and most have been stable, including 2 followed for >30 years. In the 72 patients operated on, there were 15 perioperative and 5 late deaths. Operations consisted of VSD closure alone in 7, VSD closure and valvuloplasty in 50 and VSD closure and aortic valve replacement in the other 15. Valvuloplasty was more effective in those operated on under age 10 compared to those older than 15 years (46 vs 14%). The durability of the valvuloplasty was 76% at 12 years and 51% at 18 years.

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Aortic regurgitation (AR) in association with ventricular septal defect (VSD) is uncommon, the incidence being 5.5% in the United States.¹ Detailed studies have identified the VSD location to be either subcrystal or subpulmonary, with valve prolapse being present in most.²⁻⁷ Subpulmonary VSD is more common in oriental races,^{2,3,7-9} while subcrystal VSD predominates in caucasian races.^{1,10-12} AR is an acquired lesion that is progressive in some while remaining mild in others. A number of surgical valvuloplasty techniques to alleviate AR have been described with varying results^{5,10,13,14} and present an attractive alternative to aortic valve replacement. While those with severe AR require surgery, the optimal management of patients with mild to moderate AR remains controversial, especially in teenagers and adults. This study evaluates onset and progression of AR, VSD location, cusp prolapse, infective endocarditis and surgical results.

METHODS

From 1946 to March 1989, 92 patients (33 women and 59 men) were seen with VSD and AR. All had a murmur of AR and were catheterized at least once, preoperatively. Patients with other complex lesions such as subaortic stenosis, tetralogy of Fallot and those who developed AR after endocarditis or after surgical VSD closure, were excluded. All available data, including clinical, angiographic, surgical and autopsy information were reviewed in detail.

The VSD location was classified as the following: subpulmonary (the superior margin being at or close to the pulmonary valve); subcrystal (paramembranous), recognizing that some of the subcrystal extended into the conal septum; or unknown. For comparison purposes, VSD locations among 222 patients with uncomplicated VSD from our own angiographic files (1975 to 1980) were determined.

AR was documented by angiography in 75 and at surgery in the other 17 patients. The degree of AR was considered mild, moderate or severe based on angiography. Clinically, if the murmur intensity was \leq grade 2 with a pulse pressure of <50 mm Hg, AR was considered mild. If the murmur was \geq grade 3 and pulse pressure ≥ 75 mm Hg, AR was considered severe. All others were deemed moderate. Progression of AR was defined based on angiography alone or an increase in ≥ 2 of the following: murmur intensity; pulse pressure (by $>50\%$); or cardiothoracic ratio on x-ray (by $\geq 10\%$).

In terms of surgery, 72 patients underwent ≥ 1 intra-cardiac procedure by 7 cardiac surgeons at our institution, including 3 operated on elsewhere. Cardiopulmonary bypass was used in all. The VSD was closed by suture in 35 and with a patch in 36, the defect having closed spontaneously in the other patient. The route of closure was via the right ventricle in 41, the right atrium in 12, the aorta in 13, the pulmonary artery in 2 and unknown in the other 3. The valvuloplasty methodology varied throughout the years, but, from 1973, the technique used in most has been similar to that introduced by Plauth⁶ and Frater⁷ with modifications as described by Trusler.¹⁰ Variation in the level of cusp attachment in some required further modifications. Exploration for a patent ductus arteriosus (repeated in 1) because the

murmurs were considered continuous was undertaken in 8 patients (all but 1 before 1965) with 1 death.

Statistical analyses: To compare groups with respect to measured variables, T tests were used. The chi-square statistic was used to test for differences in proportions. Those 9 patients in whom VSD location was unknown were excluded from the statistical analyses. Actuarial analyses were carried out using the method of Kaplan and Meier.

RESULTS

Aortic regurgitation onset: The murmur of AR appeared during follow-up in 65 patients at ages of 0.5 to 17 years (median 5.3). Among these, the VSD was subcrystal in 43, subpulmonary in 15 and unknown in the

FIGURE 1. Actuarial analysis identifying the probability of progression of mild aortic regurgitation.

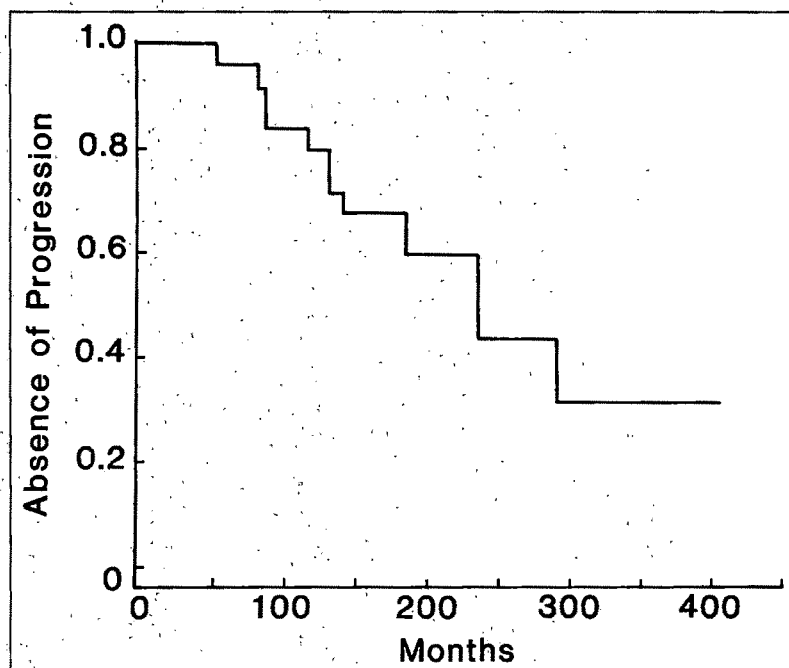
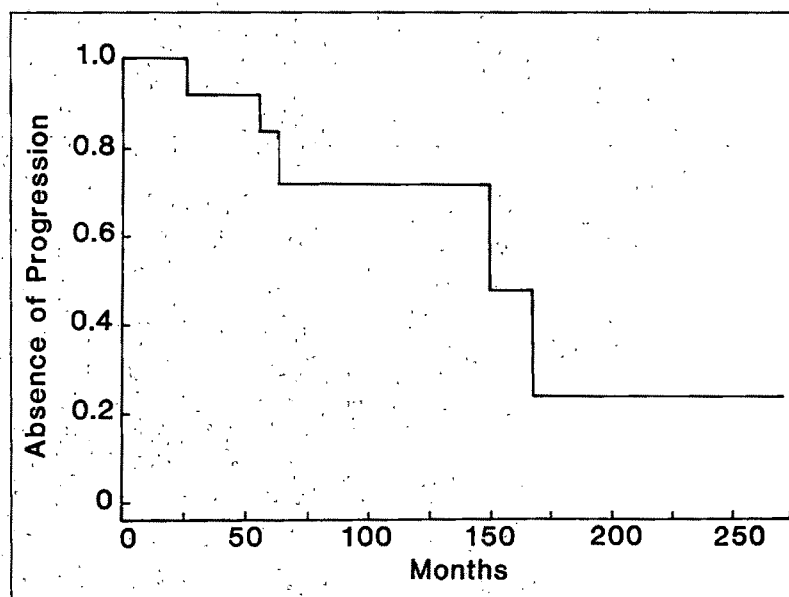


FIGURE 2. Actuarial analysis identifying the probability of progression of moderate aortic regurgitation.



other 7, with the median AR onset ages being similar in the 3 groups.

Aortic regurgitation progression: There were 58 patients followed medically for 0.1 to 35 years (median 6) after AR appeared. At the diagnostic catheterization, AR by angiography was mild in 30 patients, moderate in 19 and severe in the other 9.

MILD AORTIC REGURGITATION: During follow-up from 1 to 35 years (median 11), AR progressed in 9 (30%) (Figure 1).

MODERATE AORTIC REGURGITATION: During follow-up from 1 to 23 years (median 4), AR progressed in 5 (26%) (Figure 2).

SEVERE AORTIC REGURGITATION: During follow-up from 0.1 to 21 years (median 4), further progression in terms of increasing AR murmur intensity and pulse pressure occurred in 3 patients (33%).

Thus, although there was no significant difference in progression rates between these groups ($p = 0.1$), over-

all AR progressed in 17 patients (29%), while remaining unchanged in the other 41 (71%) during a median follow-up period of 6 years. Relative to VSD location, progression occurred in 13 of the 41 (32%) patients, with a subcrystal defect compared to 1 of 12 (8%) with a subpulmonary lesion and 3 of 5 (60%) of those with a VSD of unknown type.

Ventricular septal defect: The VSD in the 83 patients in whom location was known was subcrystal in 62 (75%) and subpulmonary in 21 (25%). This was significantly different ($p = 0.001$) when compared to our 222 patients with an uncomplicated VSD, where the defect was subcrystal in 170 (76%) and subpulmonary in 12 (5%). Thus, the probability of AR developing was 2.5 times more likely in those with a subpulmonary VSD compared to those with a subcrystal VSD.

Aortic valve: Among 90 patients in whom the number of cusps could be ascertained, the valve was tricuspid in 81 (90%) and bicuspid in 9 (10%). Prolapse of

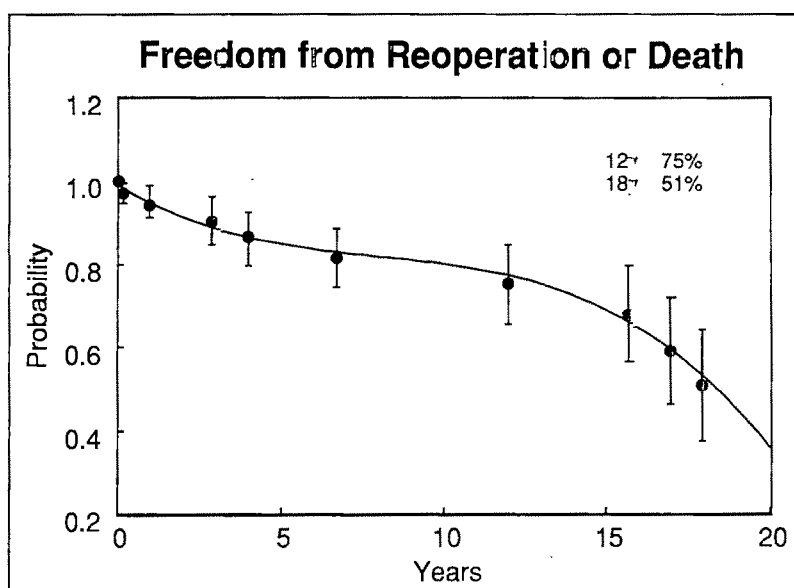


FIGURE 3. Actuarial analysis of durability of valvuloplasty, showing probability of remaining free of reoperation or death to be 76 and 51% at 12 and 18 years post-operatively, respectively (95% confidence level ± 1 standard deviation).

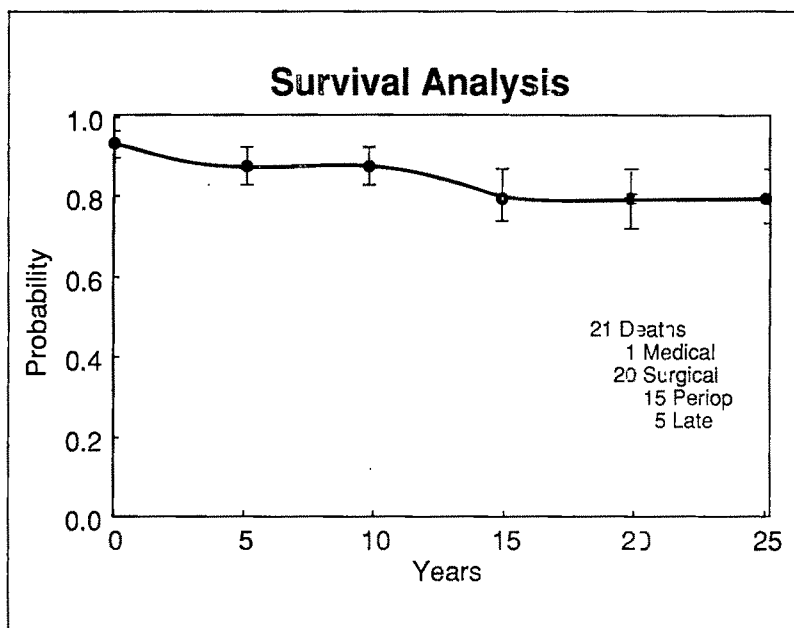


FIGURE 4. Actuarial analysis identifying probability of survival 80% at 25 years (95% confidence level ± 1 standard deviation).

≥1 cusp was present in 81 patients (Table I), occurring in 90% of those with a subcrystal VSD and in all with a subpulmonary VSD (difference not significant). The noncoronary cusp prolapsed alone in 11 patients, all with subcrystal VSD. Left coronary cusp prolapse did not occur in any. Among those 9 patients with a bicuspid valve, the VSD was subcrystal in 6, subpulmonary in 2 and unknown in the other, with prolapse being evident in 3.

A right aortic arch was present in 7 patients (8%), among whom the VSD was subcrystal in 4, subpulmonary in 1 and unknown in the others.

Pulmonary stenosis: There were 42 patients with a peak gradient of ≥10 mm across the right ventricular outflow tract. The gradient was valvar in 16 (range 10 to 47 mm Hg; median 18) and subvalvar in the other 26 (range 12 to 55; median 25 mm Hg), of whom 9 had a double-chambered right ventricle. In 7 of these latter patients, progression of obstruction was identified at repeat catheterizations, the VSD being subcrystal in 4, subpulmonary in 2 and unknown in the other.

Pulmonary-systemic flow ratio (Qp:Qs): At catheterization, when AR was present, the Qp:Qs ranged from 1 to 4 (median 1.6), the median values being similar for subcrystal VSD and subpulmonary VSD. The pulmonary artery mean pressure ranged from 4 to 36 (median 15) and no patient had pulmonary vascular obstructive disease.

Infective endocarditis: Infective endocarditis occurred 17 times, without mortality, in 14 patients, an incidence of 15 episodes per 1,000 patient years, being 21/1,000 in unoperated patients and 9 in those after surgery. Thirteen episodes occurred before and 4 episodes occurred postoperatively at age 4 to 36 years (median 19). The causative organism was alpha streptococcus (6), beta streptococcus (1), *Staphylococcus aureus* (6) and was unknown in the other 4. The aortic valve was tricuspid in 13 patients. The infection resulted in severe AR in 2 patients, both requiring valve replacement, 1 of whom sustained an embolic hemiplegia and a later repeat valve replacement because of a second episode of endocarditis.

Medical management: There were 20 patients followed medically with 1 death, this occurring suddenly in a 14-year-old with severe AR awaiting surgery in 1959. The other 19, now age 8 to 44 years (median 22), have been followed for 297 patient years (median 15). Among these, the VSD is subcrystal in 12 and subpulmonary in 7. All are asymptomatic with progression of the AR being evident in 5 (26%). Clinically, the degree of AR is considered mild at most in 9, moderate in 9 and severe in the other. Among those with mild AR are 2 patients with subpulmonary VSD who have been followed for 32 and 35 years, respectively, 1 of whom has had 2 uncomplicated pregnancies. In another patient with a bicuspid valve and moderate AR at age 44 years, the VSD has closed spontaneously.

Surgical management: VENTRICULAR SEPTAL DEFECT CLOSURE ALONE: There were 7 patients (subcrystal 6, subpulmonary 1) who underwent VSD closure alone at age 6 to 24 years (median 8), 3 of whom had bicuspid aortic valves. Preoperatively, AR was mild in 6 patients and

TABLE I Ventricular Septal Defect Location and Aortic Valve Prolapse

VSD Location	AoV Prolapse (%)					
	n (%)	RCC	NCC	RCC&NCC	LCC	Absent
Subcrystal	62 (67)	34 (55)	11 (18)	11 (18)	0	6 (9)
Subpulmonary	21 (23)	18 (86)	0	3 (14)	0	0
Unknown	9 (10)	4 (44)	0	0	0	5 (56)
Total	92	56 (61)	11 (12)	14 (15)	0	11 (12)

AoV = aortic valve; LCC = left coronary cusp; NCC = noncoronary cusp; RCC = right coronary cusp; VSD = ventricular septal defect.

TABLE II Ventricular Septal Defect Closure and Aortic Valvuloplasty

	1946 to 1973 (n = 30)		1973 to 1989 (n = 20)	
Op age (yrs)	3 to 25 (median 9)		2 to 25 (median 7)	
Follow-up (yrs)	1 to 29 (median 16)		0.1 to 11 (median 4)	
Death	17		0	
Periop	13		0	
Late	4		0	
AR	Preop	Follow-Up	Preop	Follow-Up
None	0	2	0	5
Mild	4	5	6	7
Moderate	5	8	9	5
Severe	8	2	5	3
AVR	Preop	Follow-Up	Preop	Follow-Up
Periop	0		2	
Late	1		1	

AR = aortic regurgitation; AVR = aortic valve replacement; op = operation; periop = perioperative.

TABLE III Ventricular Septal Defect Closure and Aortic Valve Replacement

	<1973 (n = 5)		>1973 (n = 10)	
Op age range (yrs)	4 to 24 (median 16)		2 to 30 (median 19)	
Deaths	2		1	
Periop	2		0	
Late	0		1	
Follow-up (yrs)	5 to 19 (median 11)		2 to 14 (median 7)	
	Preop	Follow-Up	Preop	Follow-Up
AR				
None	0	1	0	5
Mild	0	1	0	3
Moderate	1	1	4	1
Severe	4	0	6	0
AVR				
Periop	0		2	
Late	0		2	

Abbreviations as in Table II.

severe in 1 in whom a calcified right coronary cusp did not allow valvuloplasty at the age of 13 years. All survived and at 1 to 24 years of follow-up (median 9), AR was absent in 2 patients, mild in 4 (including the patient with the calcified cusp) and was moderate in the other.

VENTRICULAR SEPTAL DEFECT CLOSURE AND VALVULOPLASTY: This was the initial procedure in 50 patients (Table II). Before 1973, this was undertaken in 30, with 13 perioperative deaths. Since 1973, there have been no deaths among 20 patients thus managed.

The 37 early survivors were followed for 0.1 to 29 years (median 7). Compared to preoperatively, AR was absent in 7 patients (19%), decreased in 12 (32%), was

unchanged in 11 (30%) and increased in the other 7 (19%). Valve replacement became necessary in 4 patients, 2 undertaken early postoperatively because of severe AR and hemolysis, with severe central nervous system injury occurring in 1. There were 4 late deaths, 3 occurring suddenly in patients with severe AR; the other was noncardiac, in a patient with mild AR.

Since 1973, the incidence of mild or no AR after surgery has increased, although follow-up is clearly shorter. A decrease in AR postoperatively was evident in 46% (12 of 26) of those operated on at <age 10 years compared to only 4% (2 of 14) of those operated on at >age 15 years ($p = 0.044$). Since 1973, the respective values were 55% (6 of 11) and 0% (0 of 4) compared to 40% (6 of 15) and 20% (2 of 10) before that year. In terms of durability of the valvuloplasty, the probability of remaining free of reoperation or death was 76 and 51% at 12 and 13 years postoperatively, respectively (Figure 3).

VENTRICULAR SEPTAL DEFECT CLOSURE AND AORTIC VALVE REPLACEMENT: The ages at surgery in these 15 patients ranged from 2 to 30 years (median 16). There were 2 perioperative deaths and 1 late death (Table III). At follow-up of 2 to 19 years (median 7), AR was absent in 6 patients (43%), mild in 4 and moderate in the other 2. Repeat valve replacement was necessary in 2 patients because of stenosis in 1 and stenosis with regurgitation of a porcine prosthesis in the other.

DEATHS: There were 20 deaths (15 perioperative, 5 late), 19 occurring among patients operated on before 1973. The remaining patient died 12 years postoperatively due to thrombosis of a prosthetic valve after omission of anticoagulant therapy. All but 1 of the 20 patients had severe AR preoperatively. The probability of survival at 25 years was 80% (Figure 4).

DISCUSSION

Anatomical features: In uncomplicated VSD in this country, the autopsy location was subcrystal in 70% and subpulmonary in 8%,¹⁵ similar to our angiographic findings and in contrast to 49 and 17%, respectively, in Japan.³ In Western VSD surgical series, AR has been noted in 2.2 to 12%^{11,12} with the VSD being subcrystal in 71% and subpulmonary in 29% of patients with AR. In oriental VSD surgical series, AR occurred in 7 to 13% with the VSD being subcrystal in 20% and subpulmonary in 80% of those with AR.^{2,7-9,25} In this series, the respective values were 75 and 25%, with development of AR being 2.5 times more likely among those with a subpulmonary defect. Regardless of race in VSD with AR, men are more commonly affected,^{4,5,9,11,12,16-24} being 64% in this series in contrast to 49% in uncomplicated VSD.²⁵ In terms of cusp prolapse, our data are comparable to those previously reported, with the right cusp involved in most and in all with a subpulmonary VSD. Noncoronary cusp prolapse alone occurred only in those with a subcrystal defect while left cusp prolapse was not seen in any. Bicuspid valves, including our own, have been reported in 5% of surgical patients, the VSD being subpulmonary in one third of these.^{3,9,16,24} Pulmonary stenosis, valvar and subvalvar, noted in other se-

ries^{2,4,5,8-12,19-21,24} was present in 46% of our patients, with obstruction being progressive in almost all with a double-chambered right ventricle. Similar to other reports, the pulmonary systemic flow ratio was low (median 1.6) and none had vascular obstructive disease.^{12,20,23}

Aortic regurgitation onset and progression: Our data confirm that AR is acquired. Our earliest onset age was 6 months.⁹ The median onset ages reported ranged from 5.5 to 14 years,¹² ours being 5.3 years, similar to Japan.⁷ Among adults, a median age of 36 years has been observed in 10% of VSD patients, although only 2 of 10 had a murmur and no prior history of endocarditis.¹⁷ Progression of AR, rapid in some, was noted in 56% by Plauth⁵ and in 52% by Nadas,⁴ being slow in most over 5 to 10 years. An increase in 36% of those with mild AR over 6.5 years and in 11% of moderate AR over 3.5 years was observed by Karpawich¹⁶ and in 17% during a 13-year period by Halloran.¹¹ In this series, overall, 29% progressed during a median of 6 years; among 19 followed medically for a median 15 years, progression has occurred in 26%, although remaining mild in 47%, 2 of whom have been followed for 32 years or more.

Endocarditis: In uncomplicated VSD, the occurrence rate is 1.5/1,000 patient years.²⁶ In our series, the rate was 15, 21 in medically and 9 in surgically managed patients. Of approximately 50 episodes reported in the literature and including our own, 88% occurred preoperatively, with 1 death and severe AR in 2, and 12% postoperatively, with 3 deaths and severe AR in another. Thus, while endocarditis is more common in unoperated patients, surgery does not eliminate this risk.

Surgical results: It must be emphasized that this review period covers the entire cardiac surgical era and that advances have been such that mortality rates are now almost zero.

In terms of surgical management in the reports reviewed^{1,3,5,8-14,16,19,21-24,27-30} and including our own, VSD closure alone was carried out in 197 patients, most with mild AR, with 7 early deaths (4%). AR was reduced in 61%, including 44% in whom it was eliminated. Where data were available, AR was improved in subcrystal defects in 15 of 39 (38%) patients, including complete relief in 7 of 29 (24%) in subpulmonary defects in 13 of 23 (57%) and 11 of 27 (41%), respectively. Although patient numbers are small, they suggest that VSD closure alone was more effective in those with a subpulmonary VSD. Valvuloplasty procedures in addition to VSD closure were carried out in 368 patients in the reports reviewed, including our own, with 30 early deaths (8%). From available data, AR was improved in 70%, including 32% in whom it was eliminated. Age at operation ranged from 2 to 35 years (mean 12.7) and follow-up from 0.1 to 29 years (mean 3.8). More satisfactory decrease of AR has been reported among younger patients,⁹ while in another series, it was more effective in patients over age 5 years than in those younger.¹⁶ In our own data, results were better among those under age 10 years compared to those over 15 and in those operated on since 1973, with the probability of remaining free of reoperation or death being 76% at 12 years

TABLE IV Surgical Results in Series with >25 Patients

Reference	Total No. of Patients	VSD Closure (%)				VSD Closure and VP (%)				VSD Closure and AVR (%)			
		n	ED	No AR	Less AR	n	ED	No AR	Less AR	n	ED	No AR	Less AR
1	40	14	0	29	86	20	25	33	U	6	66	U	U
3	85	57	0	U	65	13	U	U	69	15	U	U	87
8	76	17	0	100	100	49	6	41	76	10	30	100	100
11	27	7	0	0	29	18	17	9	55	2	50	U	100
12	51	25	8	U	50	13	8	0	50	13	15	U	85
25	35	11	27	88	88	16	6	67	U	8	25	80	U
29	25	0	0	0	0	25	0	24	68	0	0	0	0
30	64	0	0	0	0	64	2	55	7	0	0	0	0
Present	72	7	0	29	43	50	26	19	51	15	13	46	92
Total	411	138	8	61	63	268	15	33	57	69	20	67	90

ED = early deaths; U = unknown; VP = valvuloplasty VSD = ventricular septal defect; other abbreviations as in Table II.

and 51% at 18 years postoperatively. Valve replacement and VSD closure in the series reviewed, including our own, were undertaken initially in 89 of 592 operations (15%) with 16 early deaths (18%). Where information was available, AR was improved in 84%, including 67% in whom it was eliminated. These patients in general were older than those in the other 2 groups. Overall results of these 3 methods of management in a series with ≥ 25 patients are listed in Table IV. It may be seen that early mortality was least among the VSD closure group and more effective AR relief was accomplished in the valve replacement group.

It is difficult to make recommendations for management of this uncommon lesion, based on data collected over 40 years. Nevertheless, we would suggest that any subpulmonary VSD in the first decade of life should be closed. In addition, in this age group, any patient with audible AR should be operated on regardless of AR severity or VSD location. A valvuloplasty will be necessary in virtually all with moderate or more AR. In those older than 15 years, we suggest continued medical observation where AR is stable and moderate or less. Clearly any patient with severe AR requires surgery regardless of age. Strict endocarditis prophylaxis is essential. With regard to the type of procedure, in the last analysis the final decision is a surgical one. VSD closure alone may be undertaken in those with mild AR, recognizing that many will have some, albeit less, AR. A valvuloplasty will be necessary in the majority and, while residual AR is less in only half, the durability is 76% at 12 years. Valve replacement as a primary procedure should be undertaken only as a last resort.

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Frequency and Prognosis of Arrhythmias After Operative "Correction" of Tetralogy of Fallot

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Two hundred twenty-four consecutive patients operated on for tetralogy of Fallot were followed from 1 to 28 years (mean 11). Mean age at surgery was 5.3 years (range 1 to 14). Postoperative right ventricular systolic pressure was 60 mm Hg in 19 of 213 patients (9%). Fourteen patients (6%) had ventricular premature complexes on surface electrocardiograms. Seventy-nine patients underwent treadmill exercise tests, and ventricular premature complexes were induced in 17 (22%). Twenty-four-hour ambulatory monitoring in 92 patients demonstrated significant ventricular arrhythmias (\geq grade 2 of the Lown classification) in 41 (45%). The frequency of ventricular arrhythmias correlated with length of follow-up and duration of cardiopulmonary bypass. No correlation was found with age at surgery, postoperative right ventricular systolic pressure and importance of conduction defects on electrocardiogram. There were no sudden or unexpected deaths during follow-up.

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Ventricular arrhythmias are common after repair of tetralogy of Fallot and have been recognized as a risk indicator for sudden death, which has been reported in up to 5% of patients.¹⁻⁵ Whether all patients with ventricular arrhythmias should receive antiarrhythmic treatment or whether treatment should be reserved for patients with additional risk factors is still unresolved. This study reports our experience with patients operated on for tetralogy of Fallot in our institution, with special attention paid to frequency and prognosis of ventricular arrhythmias managed with an overall conservative approach.

METHODS

Two hundred twenty-four consecutive patients who underwent correction of tetralogy of Fallot from 1960 to 1986 at Sainte-Justine Hospital and who were followed for >1 year were reviewed. All patients were operated on by the same surgical team. A systemic-to-pulmonary artery anastomosis had been created before corrective surgery in 139 patients; primary repair had been done in the others. Clinical status was determined in 207 patients (93%) (clinical assessment in 197, phone evaluation in 10) during the 18 months before the end of the study (17 patients were lost to follow-up); 203 of those clinically assessed (98%) were in functional class I or II of the New York Heart Association. On chest roentgenogram the heart was usually of normal size or slightly enlarged; the mean cardiothoracic index was 0.52 ± 0.07 . Age at corrective surgery ranged from 1 to 14 years (mean 5.3). Duration of postoperative follow-up from surgery to evaluation was 1 to 28 years (mean 10.6).

A second intracardiac procedure had been performed in 6 patients (3 for outflow tract aneurysm, 2 for residual ventricular septal defect, 1 for subaortic stenosis). Right ventricular systolic pressure measured at the end of the surgical procedure after hemodynamic stabilization was available in 209 patients. In 38 patients postoperative cardiac catheterization had been done 6 months to 26 years after correction. A good correlation with a sensitivity of 89% was found between immediate postoperative right ventricular systolic pressure and pressure measured at postoperative cardiac catheterization.⁶

Twelve-lead electrocardiograms recorded preoperatively, postoperatively and at each follow-up visit (average 0.9 per year) were reviewed, with special attention given to the presence of arrhythmias or conduction defects. Complete right bundle branch block was defined as a QRS duration >0.10 second in patients younger

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than 16 years of age and >0.12 second in older patients. Left axis deviation was defined as a QRS mean frontal plane axis between -30 and -120° .

Treadmill exercise test to maximal tolerance was performed using the Bruce protocol in 79 patients. The electrocardiogram was displayed on an oscilloscope and observed for rhythm during and for 5 minutes after exercise. The test was considered positive if it induced ≥ 1 ventricular premature complex. The mean age at surgery of this group of patients was 5.6 years with a mean follow-up of 12.6 years.

Twenty-four-hour ambulatory monitoring was performed in 92 patients; in 85 patients it was done during 18 months before the end of the study. All patients were studied as outpatients. These patients do not differ from the total group for mean age at surgery (5.4 years) and mean follow-up duration (11.4 years). Ventricular arrhythmias were graded using a modification of Lown's criteria⁷ proposed by Deanfield et al⁸: grade 0 = no ventricular premature complex; grade 1 = uniform ventricular premature complexes with a peak hourly count <30 ; grade 2 = >30 ventricular premature complexes in any hour; grade 3 = couplets or multiform ventricular premature complexes with a peak hourly count <30 ; grade 4 = couplets or multiform ventricular premature complexes >30 in any hour; and grade 5 = ventricular tachycardia defined as ≥ 3 consecutive ventricular premature complexes with a mean rate $>110/\text{min}$. Ventricular arrhythmias were considered significant when \geq grade 2.

Since 1986, 9 patients have been treated with phenytoin for significant ventricular arrhythmias. The mean duration of treatment from beginning to the last evaluation was 1.3 years.

Statistical significance of proportions was determined by Fisher's exact test and means by unpaired Student's *t* test. Analysis of covariance was also used to take into account the possible confounding effects of co-variables. A *p* value <0.05 was considered significant.

TABLE I Comparison of Clinical Data in Patients With and Without Exercise-Induced Ventricular Premature Complexes

	VPCs During Exercise (n = 17)	No VPCs During Exercise (n = 62)	p Value
Age at repair (yrs)	6 \pm 2	5.5 \pm 2.0	NS
Age at treadmill test (yrs)	19 \pm 6	16 \pm 7	NS
Years post-op at treadmill test	13 \pm 6	10 \pm 6.5	NS

NS = not significant; VPC = ventricular premature complex.

RESULTS

Late deaths: There were no sudden or unexpected deaths during follow-up. Four patients died 4 to 17 years after surgery, 3 from intractable heart failure and 1 from massive hematemesis.

Ventricular premature complexes on electrocardiogram: Fourteen of the 224 patients (6%) had at least 1 electrocardiogram showing ventricular premature complexes. One of these patients died from intractable heart failure 4 years after surgery. Follow-up of these patients ranged from 4 to 25 years (mean 13.6).

Treadmill exercise test: Exercise-induced ventricular arrhythmias occurred in 17 of 79 patients (21.5%). They were detected only during the immediate recovery period in 6 patients, during exercise only in 3, and both during exercise and recovery in 8. In 3 patients ventricular premature complexes, present at rest, disappeared with exercise. These are the only 3 of the 14 patients with ventricular premature complexes on electrocardiogram who underwent stress testing. Patients with ventricular arrhythmias were older at the time of the treadmill test and had a longer postoperative follow-up than those without ventricular arrhythmias although the differences were not statistically significant. Age at cardiac repair was not significantly different between the 2 groups (Table I).

FIGURE 1. Distribution according to Lown's classification of the 92 patients who underwent Holter monitoring. For classes 3 and 4, solid bars represent patients with couplets.

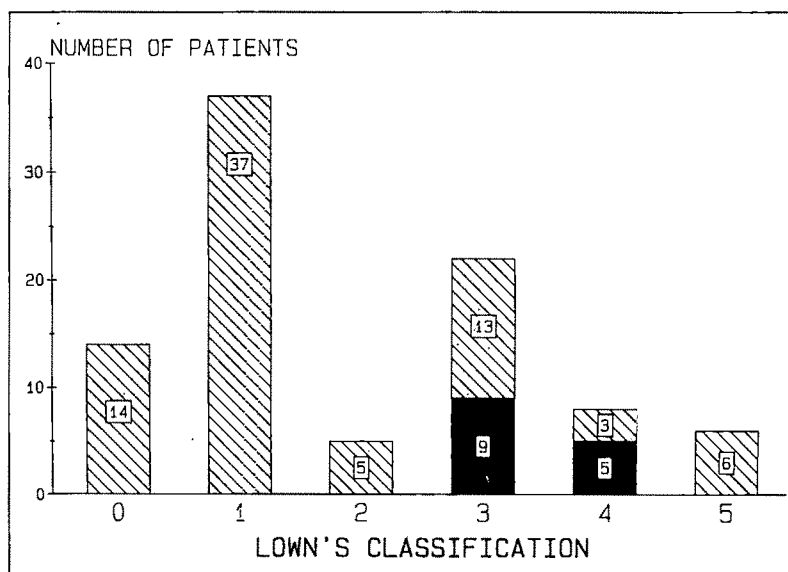


TABLE II Risk Factors for Significant Ventricular Arrhythmias Detected by Ambulatory Monitoring

	Significant Arrhythmias (n = 41)	No Significant Arrhythmias (n = 51)	p Value
Age at surgery (yrs)	5.5 ± 1.5	5.4 ± 2.2	NS
Age at AM (yrs)	17.6 ± 7.0	16.4 ± 9.0	NS
Years postop at AM	12.1 ± 6.0	10.9 ± 8.0	NS
>10 yrs (%)	26 (63)	21 (41)	<0.05
Previous shunt (%)	27 (66)	32 (63)	NS
Outflow patch (%)	32 (78)	36 (71)	NS
Reoperation (%)	1 (2)	4 (9)	NS
Duration of CPB (min)	106 ± 20	98 ± 20	<0.05
>90 min (%)	34 (83)	32 (62)	<0.05
Postop RVSP (mm Hg)*	48 ± 13	47 ± 14	NS
>60 mm Hg (%)	4 (11)	5 (11)	NS

* Available in 38 patients with and in 47 patients without significant arrhythmias.

AM = ambulatory monitoring; CPB = cardiopulmonary bypass; NS = not significant; RV SP = right ventricular systolic pressure.

Twenty-four hour ambulatory monitoring: Distribution of these 92 patients according to Lown's classification is shown in Figure 1. Ventricular arrhythmias \geq grade 2 of Lown were found in 41 patients (45%). Sustained ventricular tachycardia was not detected in any patient. Operative and hemodynamic characteristics of the 2 groups were compared and are listed in Table II. The incidence of arrhythmias was significantly higher when follow-up was >10 years and duration of cardiopulmonary bypass >90 minutes. Seven of 26 patients (27%) had significant ventricular arrhythmias when duration of cardiopulmonary bypass was <90 minutes, as opposed to 52% (34 of 65) when it was >90 minutes ($p < 0.005$). Cardiopulmonary bypass duration was not related with the year of surgery ($r = 0.09$). For duration of follow-up and cardiopulmonary bypass, analysis of covariance could not demonstrate any difference between patients with ventricular arrhythmias versus those without ventricular arrhythmias taking into account the age at surgery. There was no correlation between the importance of conduction defects and the presence of significant ventricular arrhythmias (Table III).

Treatment with phenytoin: Nine patients had been treated with phenytoin because of significant ventricu-

lar arrhythmias on ambulatory monitoring. Ventricular premature complexes were also present on surface electrocardiograms in 5. Four patients had palpitations. No difference was found between the modified Lown's classification of these 9 patients compared to the 32 untreated patients with significant arrhythmias. Treatment was successful in 7 of 9 patients. There was no difference between postoperative right ventricular systolic pressure of treated and nontreated patients with significant ventricular arrhythmias (49 ± 16 vs 47 ± 13 mm Hg).

DISCUSSION

Significant ventricular arrhythmias were present in 45% of our patients who underwent ambulatory monitoring. This high incidence is similar to that generally reported.^{3,5,8,9} In this study, the occurrence of ventricular arrhythmias was correlated with duration of cardiopulmonary bypass. Indeed, a cardiopulmonary bypass duration >90 minutes almost doubled the incidence of arrhythmias. Cardiopulmonary bypass duration was not related to the year of surgery. Thus, since all patients have been operated on by the same surgical team, duration of cardiopulmonary bypass was almost certainly related to the severity of the malformation itself and not to the experience of the surgical team. Other factors such as conduction defects,³ age at surgery,^{5,8-10} prior systemic-to-pulmonary shunt¹¹ and postoperative right ventricular systolic pressure,^{9,11,12} which have been previously correlated to ventricular arrhythmias, have not shown the same relation in our study. The lack of correlation with age at surgery may be explained by the fact that 77% of our patients have been operated on between 5 and 6 years of age.

Duration of postoperative follow-up and age at evaluation were higher (although not significantly) in patients with exercise-induced ventricular arrhythmias. In addition, on ambulatory monitoring, patients with follow-up >10 years had a significant increase in the incidence of arrhythmias. This correlation between duration of follow-up and incidence of ventricular arrhythmias has already been reported^{5,8-10,13} leading to the speculation by others¹⁴ that the incidence of sudden death will be considerably higher in the future than the currently

TABLE III Conduction Disturbances in Relation to the Incidence of Arrhythmias Detected on Ambulatory Monitoring

	Significant Arrhythmias (n = 41)	No Significant Arrhythmias (n = 51)	p Value
Isolated incomplete RBBB	4	6	NS
Isolated complete RBBB	25	33	NS
First-degree AV Block + complete RBBB	4	9	NS
First-degree AV Block + incomplete RBBB	0	0	NS
Complete RBBB + LAD	6	3	NS
First-degree AV Block + complete RBBB + LAD	1	0	NS
Complete AV block			
Permanent	1	0	NS
Transient	3	3	NS

AV = atrioventricular; LAD = left axis deviation; NS = not significant; RBBB = right bundle branch block.

reported incidence of 3 to 5%. Although 45% of our patients had significant ventricular arrhythmias on ambulatory monitoring and despite 1 of the longest follow-ups reported, there were no sudden deaths in our population. This can certainly not be explained by the use of phenytoin in 9 patients. Mean duration of treatment was short in this group (1.3 years) and a similar number of patients with similar arrhythmias and similar hemodynamic results were not treated and are still alive. Furthermore, 8 untreated patients with ventricular premature complexes on their surface electrocardiogram remained asymptomatic for a mean duration of 14.9 years. Such a group has been said to be at very high risk with a rate of sudden death of approximately 30%.^{1,2,15} In addition to ventricular arrhythmias other factors are certainly implicated in the occurrence of these sudden deaths. Most patients with sudden death are reported to have a poor hemodynamic result defined by a right ventricular systolic pressure >60 mm Hg.^{1,5,11} In most studies, the rate of these poor results is around 30%.^{1,5,8} We had a 9% rate in our group of patients. This could explain, at least in part, the excellent outcome of this group.

On the basis of our findings, we believe that systematic treatment of postoperative arrhythmias has to be reconsidered. Antiarrhythmic therapy could be reserved for symptomatic patients and patients with complex ventricular arrhythmias associated with poor hemodynamic results. Further studies and longer follow-up are needed for a better understanding of the true significance of ventricular arrhythmias in postoperative tetralogy of Fallot.

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An Electrocardiographic Midterm Follow-Up Study After Anatomic Repair of Transposition of the Great Arteries

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Prospective studies of rhythm and conduction, before and after 1-stage anatomic repair of simple transposition of the great arteries, were performed on 24 survivors. Pre- and postsurgical serial standard electrocardiograms were obtained on each patient. Fourteen patients underwent perioperative 24-hour electrocardiograms; all had follow-up 24-hour electrocardiograms. Rare atrial or occasional ventricular premature complexes were detected in 3 (11%) patients before operation. After surgery, 1 patient developed right bundle branch block. Two patients developed a left bundle branch block. One patient had a QS pattern in V₆, which disappeared on follow-up electrocardiogram. Transient second-degree atrioventricular block was detected in 1 patient. A normal P-R interval and P-wave axis were present in all but 1 patient. Mild sinus bradycardia or rare atrial or ventricular premature complexes were detected in 4 of twenty-nine 24-hour electrocardiograms performed in the first 2 years after surgery. At 3 years after repair, 5 patients had a normal 24-hour electrocardiogram and 1 had low-grade ectopy (rare atrial and ventricular premature complexes). At 4 years, all 4 patients studied had normal 24-hour electrocardiograms. During a mean follow-up of 3 years, we have yet to document any symptomatic arrhythmias.

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The Mustard^{1,2} and Senning³ operations are the established surgical procedures for d-transposition of the great arteries, but the high incidence of tachy-bradyarrhythmias⁴⁻¹⁰ and sudden unexpected death¹¹⁻¹³ associated with atrial baffle repairs has prompted some surgeons to refine the anatomic repair.¹⁴⁻¹⁷ The arterial switch operation involves the transfer of the coronary arteries and sudden death has been attributed to myocardial infarction.¹⁸ Retrospective studies have shown a much lower incidence of significant tachy-bradyarrhythmias¹⁹⁻²¹ and atrioventricular conduction abnormalities²² after anatomic correction. Interpretation of these findings is complicated by the heterogeneous nature of both the patients and surgical techniques used. The purpose of this study was to determine prospectively the midterm effects of the arterial switch operation on cardiac rhythm and the conduction system before and after 1-stage anatomic repair.

METHODS

Study patients: Our study group consisted of 24 neonates who underwent successful anatomic repair for simple transposition of the great arteries, using techniques developed by Lecompte,¹⁵ Castaneda,¹⁶ their co-workers and Mavroudis¹⁷ from January 1985 through May 1989. Prospective studies on 16 patients began in July 1986. Eight patients repaired before this date were included in the study. Most of the patients had pre- and postoperative electrocardiograms and 24-hour electrocardiograms at timed intervals. Balloon atrial septostomy was performed on 18 (75%) patients. Three patients had abnormal coronary arteries and 1 had coarctation of the aorta. All patients underwent anatomic repair during the first week of life. The mean weight at operation was 2.6 kg. Twenty-three patients underwent "atrial septal defect" closure with running or mattress suture during anatomic repair. Most of the surgical procedure was performed under low-flow cardiopulmonary bypass after deep systemic hypothermia and the use of potassium-blood cardioplegic solution. The aortic cross-clamp time was <60 minutes. Eighteen patients underwent cardiac catheterization 8 to 12 months after anatomic repair. All survivors were without cardiac medications 2 to 18 months after repair.

One patient with a transversal course coronary artery (type E according to Yacoub's classification)²³ had a lethal myocardial infarction secondary to an obstructed left main coronary artery 2 months after anatomic

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TABLE I Number of 24-Hour Electrocardiographic Studies Performed During the Study

No. of Patients	53 Holter Recordings					
	Years Postoperatively					
	Preop	0*	1	2	3	4
No. of Patients	4†	10	14	15	6	4‡

* Early postoperative period (mean 35 days); † only 1 patient had study before atrial septostomy; ‡ 2 patients had only 1 study during follow-up.
Preop = before operation.

repair. Of interest, another newborn with simple transposition of the great arteries had several episodes of sudden-onset supraventricular tachycardia during cardiac catheterization before balloon atrial septostomy. He died a few hours after anatomic repair as a result of refractory supraventricular tachycardia and therefore is not included among the patients in our midterm follow-up.

Electrocardiographic follow-up: A total of 170 (average 7/patient) serial electrocardiograms were carried out in the pre- and postoperative period. These tracings were analyzed for conduction defects, P-wave morphology and patterns of myocardial misperfusion. Standard age-corrected electrocardiographic criteria were used.²⁴ In addition, 24-hour electrocardiogram monitoring studies were obtained at preset timed intervals—preoperatively and 1, 2, 3 and 4 years after surgery. All survivors had at least one 24-hour electrocardiogram study (Figure 1). Due to timing of surgery or severe illness in several patients, we had to postpone the preoperative 24-hour electrocardiogram to the early postoperative period. Four patients had a 2-channel 24-hour electrocardiogram performed before surgery and 1 before balloon atrial septostomy. Ten patients had a 24-hour electrocardiogram performed during the early postoperative period (3 days to 4 months, mean 35 days, Table I). The incidence and type of arrhythmia were analyzed with respect to age at surgery, medical treatment, residual hemodynamic abnormalities and complexity of the surgical procedure.

Analysis of data: Electrocardiographic analysis was performed by 2 observers (JV, SW). Analysis and interpretation of 24-hour electrocardiograms were done by 1 observer (JV). The 24-hour recordings were used to determine the dominant rhythm, atrioventricular conduction, the presence of brady-tachyarrhythmias and the frequency of ectopic beats.

Sinus bradycardia and a wandering pacemaker rhythm with a rate >70 beats/min in infants and 50 beats/min in older children were considered normal.²⁵ Atrial premature complexes <30/hr were classified as "rare." Ventricular premature complexes <10/hr were classified as "rare" and 11 to 30/hr as "occasional." Statistical analysis was performed using the 2-tailed *t* test. A *p* value <0.05 was considered statistically significant. All values are expressed as a mean and 1 standard deviation.

TABLE II Incidence of Arrhythmias Detected by Scalar and 24-Hour Electrocardiograms in 24 Survivors

Type ECG	No. of Patients					
	Years Postoperatively					
	Preop	0*	1	2	3	4
Scalar	2	1	0	0	0	0
24-hr	2†	3‡	2	2	1‡	0

* Early postoperative period (mean 35 days); † 1 patient had atrial premature complexes detected by scalar and 24-hour electrocardiogram; ‡ a patient with >1 arrhythmia.
ECG = electrocardiogram; Preop = before operation.

RESULTS

Occurrence of arrhythmias: Two types of arrhythmias, rare atrial and occasional ventricular premature complexes, were detected in 3 patients before anatomic repair (Table II). In addition, a 1-day-old infant with transposition of the great arteries and perinatal asphyxia who underwent an emergency cardiac catheterization developed sudden-onset supraventricular tachycardia before balloon atrial septostomy. The tachycardia was terminated with programmed atrial or ventricular extra-stimulation. After anatomic repair, he succumbed to the recurrence of a tachyarrhythmia that could not be terminated by cardioversion, programmed ventricular extrastimulation, digoxin or propranolol. No other arrhythmic deaths occurred.

In the immediate postoperative period, there were 2 types of transitory arrhythmias, second-degree atrioventricular block and supraventricular tachycardia. Three years after surgery, 1 of 4 patients who had experienced transient arrhythmias after the immediate postoperative period remained with rhythm disorders on more than one 24-hour electrocardiogram. None of 4 patients who underwent the fourth year postoperative 24-hour electrocardiogram had a significant arrhythmia during the recording.

Preoperative electrocardiogram recordings: Three (11%) patients had either rare atrial or occasional ventricular premature complexes. Normal P-R interval, P-

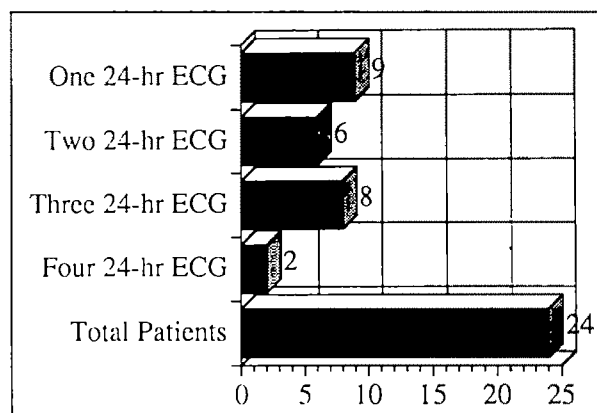


FIGURE 1. Number of 24-hour electrocardiographic studies (per patient) performed during the study. ECG = electrocardiographic monitoring.

TABLE III Results of 24-Hour Electrocardiographic Recordings Before and After Anatomic Repair

	24-Hour Electrocardiograms				
	Years After Operation				
	Preop (n = 5)	1 (n = 14)	2 (n = 16)	3 (n = 8)	4 (n = 5)
P-R interval (ms)	M 104 SD 9	116* 13	122 13	123 9	120 4
QRS duration (ms)	M 63 SD 7	68 5	69 16	79 18	76 16
Low heart rate (beats/min)	M 100 SD 14	75 22	63 10	60 6	54 4
Max heart rate (beats/min)	M 176 SD 26	172 13	164 18	150 17	150 14

* p < 0.05.

M = mean; Max = maximal; Preop = preoperative period; SD = standard deviation.

TABLE IV Arrhythmias Before and After Anatomic Repair in 24 Patients

	Scalar and 24-Hour Electrocardiograms					
	Years Post-operatively					
	Preop	0*	1	2	3	4
SVT	†	1†				
Rare APC	2‡	1‡		1	1	
Rare VPC		1‡	1‡	1	1	
Occ VPC	1					
Sinus bradycardia§			1	1		
Second-degree AV block		1‡				

* Early postoperative period (mean 35 days); † a newborn developed supraventricular tachycardia before and after anatomic repair and died; ‡ transitory arrhythmia in 1 patient; § <70 beats/min in infants or <50 beats/min in children.

AV = atrioventricular; Occ VPC = ventricular premature complexes <1 to 30/hr; Preop = before operation; Rare APC = atrial premature complexes <30/hr; Rare VPC = ventricular premature complexes <10/hr; SVT = supraventricular tachycardia.

wave axis and sinus rhythm were present in all of the electrocardiograms.

Postoperative scalar electrocardiogram: After surgery, all patients had ≥ 1 electrocardiogram for review (mean 7). One patient had intermittent, transitory second-degree atrioventricular block and Mobitz II and 1 patient had had complete right bundle branch block. A transitory left bundle branch block pattern was observed in 2 patients. Postoperative electrocardiograms revealed right atrial enlargement in 4 patients. The P-wave amplitude measured 0.1 to 0.3 mV (mean 0.17). Only 1 patient had an abnormal P-wave axis (-45°). The QRS axis was abnormal in 4 patients with right-axis deviation. One patient had an abnormal electrocardiographic pattern, qS with inverted T wave in V_6 , which normalized a few months after anatomic repair. Transient ST-T changes were observed in 7 patients.

Postoperative 24-hour electrocardiogram: There was a small but significant increase ($p < 0.05$) of the P-R interval 1 year after anatomic repair. Overall, the P-R intervals were within normal limits if corrected for age. The minimum and maximum mean heart rates fol-

low the usual tendency to decrease during the aging process of the patients (Table III). Sinus bradycardia was detected in 1 patient at 1 year and another patient at 2 years after anatomic repair (Table IV). All of the follow-up patients remained in sinus rhythm with an adequate chronotropic response to various types of activities. Junctional rhythm of >10 beats was not detected in our patients. One patient had rare atrial and ventricular premature complexes on a 24-hour electrocardiogram performed 1 week after anatomic repair. During the recording, the patient developed a brief episode of supraventricular tachycardia at a rate of 260 beats/min. The tachyarrhythmia did not recur during the follow-up period. Rare atrial and ventricular premature complexes occurred in 1 patient at the second postoperative year. One patient with atrial premature complexes before surgery had rare atrial and ventricular premature complexes at the third postoperative year (Table IV).

Influence of other factors: Several clinical factors were evaluated to determine if there was a relation with conduction or rhythm disturbances after anatomic repair. The age of the patient at the time of the operation did not appear to influence the cardiac rhythm. Balloon atrial septostomy was performed in 70% of the patients with rhythm disorders compared to 79% of arrhythmia-free patients. Only 1 patient was receiving treatment with digitalis at the onset of an arrhythmia. None of the patients with conduction or rhythm disorders had significant residual hemodynamic abnormalities. The complexity of surgery during anatomic repair may influence some of the conduction and rhythm disturbances. The patient with intermittent, transitory second-degree atrioventricular block and Mobitz II underwent closure of an atrial septal defect. The patient with complete right bundle branch block had had extensive manipulation of the right coronary artery. The incidence of late arrhythmias was similar to that of the perioperative period.

DISCUSSION

Intraatrial baffle repair has been the traditional corrective procedure for simple transposition of the great arteries. Postoperative long-term complications are common, and include baffle obstruction,^{2,8,11,26} residual intracardiac shunts^{2,9} and late onset brady-tachyarrhythmias.^{2,4-10,26} The residual ventricular-arterial discordance in patients who had the Mustard or Senning operation is associated with significant hemodynamic abnormalities and include, most importantly, right ventricular dysfunction^{2,8,12,13} and tricuspid valve insufficiency.^{2,8} Potentially lethal brady-tachyarrhythmias are the most frequent complications after intraatrial baffle repair. Some of the postoperative complications appeared to be related to factors inherent to extensive atrial surgery⁴ and chronic right ventricular stress.¹² The arterial switch operation avoids extensive atrial surgery while correcting the anatomical ventricular-arterial discordance of transposition of the great arteries. Recent improvements in surgical techniques and postoperative

care have decreased the overall mortality to levels comparable with the Mustard and Senning operations. However, the translocation of the coronary arteries in the arterial switch operation has contributed to perioperative and late mortality.^{16-18,27} Postoperative complications may well play an important role in deciding the surgical approach in a patient with transposition of the great arteries.

Patients who underwent anatomic repair have a low incidence of significant arrhythmias.^{18-22,27} Some of these arrhythmias first occurred before the operation.²¹ In our study, 3 patients had arrhythmias detected before anatomic repair. Atrial arrhythmias may be intrinsic to transposition of the great arteries.^{9,22} We had a patient who developed supraventricular tachycardia before balloon atrial septostomy and another patient in whom supraventricular tachycardia was detected a few days after surgery.

During the midterm follow-up of 3 years, we were unable to detect rhythm disturbances by scalar electrocardiogram. Asymptomatic, low-grade atrial and ventricular ectopic activity were infrequently observed in 24-hour electrocardiograms performed 1, 2, 3 and 4 years after anatomic repair. These arrhythmias were transitory in most patients and none prompted antiarrhythmic therapy. A possible cause for atrial premature complexes after anatomic repair may be atrial septal defect closure,⁵ a common operative procedure (96%) in our patients.

The frequency of rhythm and conduction disturbances after the Mustard operation varies from 13 to 100%.⁶ Sinus rhythm decreases in patients who are followed for longer periods.^{6,26} After a mean follow-up of 3 years, all of our patients remain in sinus rhythm and we have yet to document any significant bradyarrhythmias. Asymptomatic sinus bradycardia was noted in some of our patients after anatomic repair. This rhythm has been observed in unoperated transposition of the great arteries patients.²⁰ Further, some authors categorized this rhythm abnormality as benign in nature.^{25,28} This finding was in sharp contrast with the high incidence of sinus bradycardia^{5,9} and junctional rhythm^{4-7,10,26} after intraatrial baffle repair. Pacemaker therapy was not prescribed in any of our patients, but was required in 5 to 28% after the atrial baffle operation.^{5-7,11}

Different degrees of atrioventricular block have been reported in children who underwent the Mustard⁶⁻⁸ and Senning⁹ operations. Atrioventricular conduction, as expressed by the P-R interval, was normal in all of our patients after the immediate postoperative period.

Transient electrocardiographic patterns of myocardial hypoxic insult were present in our patients but without clinical consequences, except in 1 patient who died with myocardial infarction 2 months after anatomic repair. Myocardial infarction and sudden death have been reported in survivors after anatomic correction in other series.²⁹

The changes observed in the P-wave axis and amplitude after atrial baffle operations³⁰ may be due to surgical distortion of the normal atrial anatomy, an ectopic

atrial rhythm or secondary to direct trauma to the sinus node or its artery. The P-wave amplitude was normal or prominent in all of our patients and only 1 patient had an abnormal P-wave axis.

While these midterm results are encouraging, the long-term prognosis of these children remains unknown.

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Safety of Cardiac Angiography with Conventional Ionic Contrast Agents

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and the Investigators of The Philadelphia Area Contrast Agent Study*

To characterize the frequency of adverse reactions to conventional ionic contrast agents, data describing the frequency of such reactions were gathered from 4,630 diagnostic cardiac angiographic procedures. The patient population had a large prevalence of severe or unstable cardiac disease (56% had New York Heart Association class III, IV or V, 12.6% had left ventricular end-diastolic pressure >25 mm Hg and 34% had 3-vessel or left main coronary artery disease). The overall minor adverse reaction rate was 14.2%. Major adverse reactions (requiring treatment) occurred in 61 (1.3%) of procedures. All adverse reactions were managed successfully and there were no deaths. Adverse reactions were more frequent in patients with higher New York Heart Association classes and with elevated left ventricular end-diastolic pressure. The adverse reaction rate was not increased in patients with more extensive coronary artery disease, reduced left ventricular ejection fraction or reduced cardiac index. The overall adverse reaction rate was probably influenced by physician behavior. Smaller volumes of contrast agent were administered to patients with more severe cardiac disease. Six percent of procedures were abbreviated either because of an adverse reaction or of concern that a reaction might occur if the procedure were continued. As a result, the diagnostic data obtained were judged to be inadequate in 0.8% of procedures. These data demonstrate that appropriate operator caution within the highly monitored environment of the cardiac catheterization laboratory allows cardiac angiography to be performed safely with conventional ionic contrast agents in most patients. Nonionic contrast agents may offer an advantage of providing greater safety and allowing a better study completion rate in patients who are severely ill and hemodynamically precarious.

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*See Appendix.

Selective cardiac angiography and coronary angiography have been important diagnostic tools since their introduction in the late 1950s.¹⁻³ Since that time the most commonly used contrast agent has been the ionic salt of diatrizoic acid. Clinically useful formulations of this compound have osmolalities >2000 mOsm/kg,⁴ and are designated as high osmolality contrast agents (HOCAs). Shortcomings of these agents include depression of myocardial contractile function,⁵ expansion of intravascular volume⁶ and alteration of cardiac electrophysiologic function.⁷

Currently, there are 4 low osmolality contrast agents (LOCAs) (iohexol, iopamidol, ioversol and ioxaglate) available for cardiac angiography. They cause less hemodynamic and electrophysiologic disturbance⁸⁻¹⁰ and accordingly offer the promise of improved safety and efficacy. However, the degree to which LOCAs, which are considerably more expensive, actually improve the safety and efficacy of cardiac angiography has not been determined.

To determine the proper role of LOCAs in cardiac angiography, it is necessary to know the safety and efficacy of HOCAs. Furthermore, it is important to know whether certain subsets of patients are at an increased risk of an adverse reaction to an HOCA and may be more likely to benefit from a LOCA. Accordingly, we studied the frequency, severity and consequences of adverse reactions to HOCAs in diagnostic cardiac angiography.

METHODS

Study design: The Philadelphia Area Contrast Agent Study was organized in 1985 to gather information concerning the safety and efficacy of HOCAs. The 13 participating cardiac catheterization laboratories are listed in Table I, and include both university and community hospitals.

We recorded data for procedures performed between May 5, 1985, and February 28, 1986, by means of a questionnaire that was completed by the responsible angiographer immediately after the procedure. In some laboratories not all angiographers participated and data were collected only from procedures performed by participating investigators who recorded data for all the diagnostic procedures they performed during the study period. Completeness of reporting was not independently monitored, but comparison of the number of completed procedure reports with known activity levels indicated a high degree of reporting completeness. Except for 5 procedures performed with ioxaglate, all procedures were performed with HOCAs. There was no bias to se-

TABLE I Philadelphia Area Contrast Agent Study Participating Hospitals

Participating Hospitals	
Abington Memorial Hospital*	Abington, Pennsylvania
Albert Einstein Medical Center*	Philadelphia, Pennsylvania
Bryn Mawr Hospital*	Bryn Mawr, Pennsylvania
Cooper Hospital University Medical Center*	Camden, New Jersey
Crozer-Chester Medical Center*	Upland, Pennsylvania
Deborah Heart and Lung Center	Browns Mills, New Jersey
Graduate Hospital*	Philadelphia
Hahnemann University Hospital*	Philadelphia
Hospital of the Medical College of Pennsylvania*	Philadelphia
Hospital of the University of Pennsylvania	Philadelphia
Presbyterian Hospital*	Philadelphia
Temple University Hospital	Philadelphia
Thomas Jefferson University Hospital	Philadelphia
Hospital of the University of Pennsylvania†	Philadelphia

* Hospitals in which not all physicians with catheterization privileges participated.

† Data coordinating center.

lect low risk patients to receive HOCAs since LOCAs were not available for routine clinical use at this time.

Data recorded: The data items recorded for each procedure are listed in Table II. New York Heart Association functional class was recorded¹¹ with the addition of a class V representing patients in extremis at the beginning of the procedure. The study protocol did not govern procedure conduct. Thus, right-sided heart catheterization was not performed in many patients, and in some patients left ventriculography was not performed. Consequently, complete data are not available for all patients.

Cardiac index was recorded as a categorical variable using 2 categories representing normal and reduced values. Left ventricular end-diastolic pressure was similarly recorded in 3 categories representing the normal range, moderate and severe elevations. If left ventriculography was performed, the left ventricular ejection fraction was estimated and assigned similarly to 1 of 3 categories.

The study protocol stipulated that only adverse reactions attributable to contrast agent administration be recorded. A major reaction was defined as one that required treatment. This classification was made by the individual investigators. Table II lists the categories of recorded adverse reactions. The nature of the data gathering

procedure made it impractical to detect contrast agent-induced renal failure.

In addition to recording adverse reactions, we endeavored to assess examination adequacy. The angiographer recorded whether or not the examination was abbreviated (defined as failure to carry out as comprehensive an examination as originally planned). For example, if the angiographer had originally *intended* to perform left ventriculography but chose not to—either because an adverse reaction occurred or because of concern that the patient would not tolerate further contrast agent injections—the procedure was classified as “abbreviated”. If the angiographer classified a procedure as abbreviated, he or she also classified the data obtained as adequate or inadequate for clinical decision making. We gathered data concerning procedure completion during the entire study. At the midpoint of the study, interim data analysis demonstrated that procedure abbreviation was being reported only when a major adverse reaction occurred. We felt that the data collection instrument was not detecting an important aspect of procedure conduct: the abbreviation of a procedure *before* an adverse reaction occurs. Accordingly, we added a question about procedure abbreviation because of *concern* that an adverse reaction might occur if the procedure were continued. This question was answered for procedures performed during the second phase of the study.

Statistical analysis: The patient population was characterized by calculating the mean values, ranges and standard deviations of continuous variables, and the frequency distributions of categorical variables. The frequencies of reactions in the various patient categories were tabulated and 95% confidence limits for proportions were calculated.¹² Associations between patient characteristics and the frequency of contrast agent reactions were identified using a 2-tailed *t* test or analysis of variance for continuous variables and the chi-square test for categorical variables. Significance was defined as $p < 0.05$.

RESULTS

Patient population: We obtained data from 4,630 procedures. The characteristics of the patient popula-

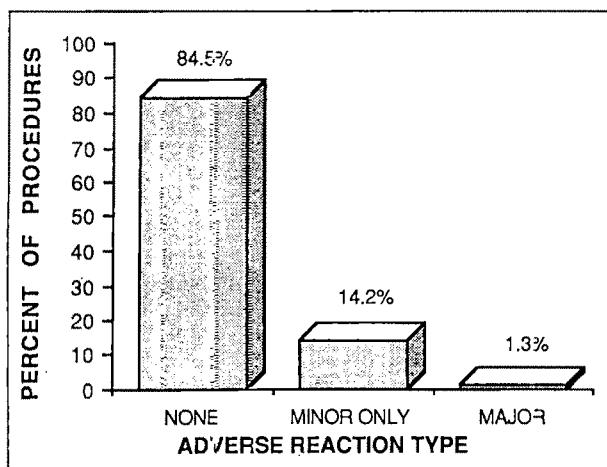


FIGURE 1. Frequency of occurrence of major and minor adverse reactions.

tion are listed in Table III. There is a large prevalence of severe and unstable cardiac disease typical of the patient population of many cardiac catheterization laboratories.

Adverse reactions to contrast agent: The frequency and types of adverse reactions are shown in Figures 1 and 2. There were no reactions in 3,911 (84%) of procedures. Minor reactions occurred in 657 (14%). There were 67 major reactions in 61 (1.3%) procedures. Thirty-four (51%) of the major reactions were alterations in systemic arterial pressure requiring treatment. Pulmonary vascular congestion occurred 23 times (34%). Anaphylactoid reactions and ventricular fibrillation were rare (2 and 8, respectively). All reactions were managed successfully and there were no deaths.

Predictors of major adverse reactions: The relations between selected variables and the frequency of major reactions are listed in Table IV and shown in Figures 3 and 4. We found significant direct relations between the major reaction rate and 2 measures of the severity of

cardiac disease: increasing New York Heart Association functional class and left ventricular end-diastolic pressure. Cardiac index and extent of coronary disease did not correlate with the reaction rate. The reaction frequency in patients with definite previous reactions was not different from that in patients without a previous reaction.

Procedure abbreviation and data adequacy: The effect of adverse reactions and the concern about possible reactions on procedure conduct are shown in Figures 5 and 6. During both phases of the study, the frequency of procedure abbreviation because of a reaction was uniform 17 of 2,823 (0.60%, 95% confidence interval 0.32 to 0.88%) in the first phase and 17 of 1,748 (0.97%, 95% confidence interval 0.51 to 1.43%) in the second phase. During the second phase 94 of 1,748 (5.4%) of procedures were reported as abbreviated for concern. Combining these data yields an overall procedure abbreviation rate of 6.1%; 5.4% of procedures were abbreviated because of concern and 0.7% of procedures (34 of

FIGURE 2. Frequency distribution of the types of major adverse reactions. ANAPHYL. = anaphylactoid reaction with circulatory collapse; HYPERTN. = hypertension; HYPOTN. = hypotension; PULM. CONG. = pulmonary vascular congestion; V. F. = ventricular fibrillation.

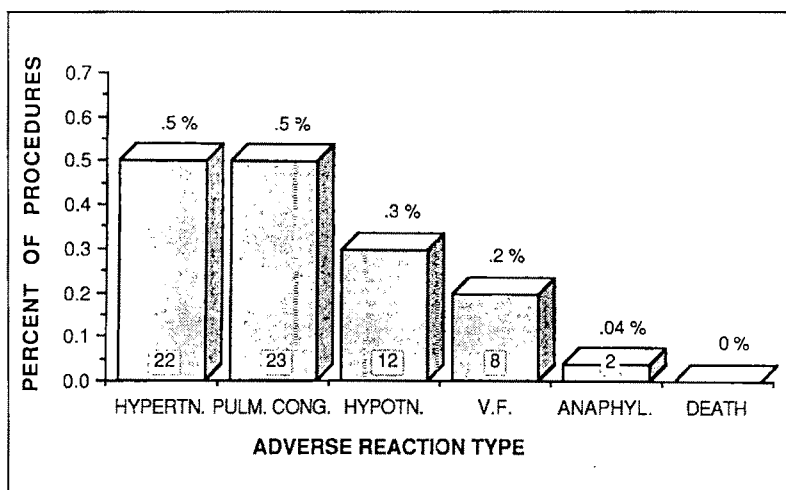


FIGURE 3. Relation between New York Heart Association functional class and the frequency of major adverse reactions.

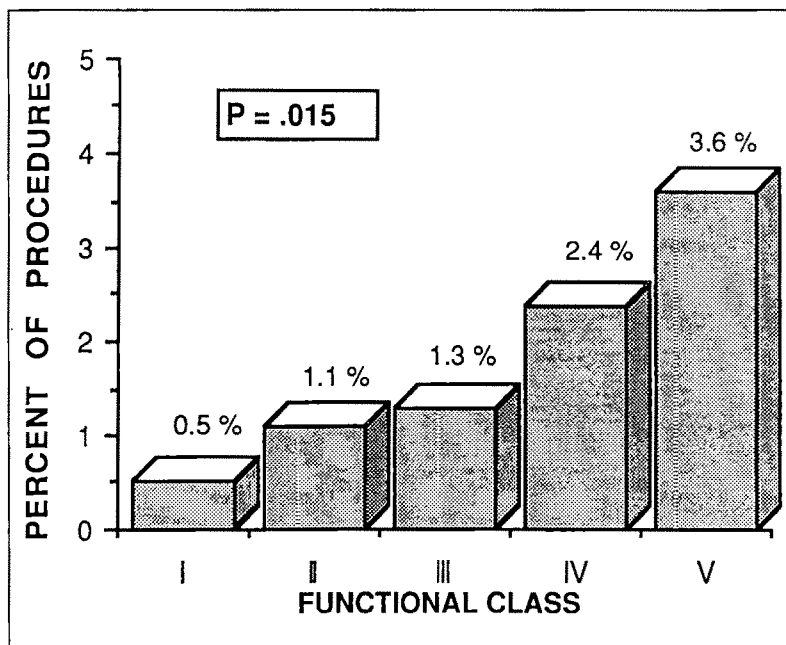


TABLE II Data Recorded

Parameter	Units/Categories
Clinical	
Gender	M, F
NYHA functional class	I, II, III, IV, V
Diabetes	No, Diet, Insulin
Hemoglobin	g/dl
BUN	mg/dl
Previous contrast agent reaction	No, Possible, Definite
Procedural	
Preprocedural steroid prep	Yes, No
Contrast agent used	Brand Name
Volume of contrast agent administered	ml
Hemodynamic and angiographic	
Normal	Yes, No
Valvular disease	Yes, No
Cardiomyopathy	Yes, No
No. of diseased coronary vessels	0, 1, 2, 3, Left main
Cardiac index	≤ 2.5 , > 2.5 liters/min/m ²
Left ventricular end-diastolic pressure	< 16 , 16–25, > 25 mm Hg
Estimated ejection fraction (%)	< 35 , 35 to 50, > 50
Adverse reactions	
None	Yes, No
Minor	
Nausea	Yes, No
Vomiting	Yes, No
Urticaria	Yes, No
Rubor	Yes, No
Sneezing	Yes, No
Angina	Yes, No
Major	
Hypertension requiring treatment	Yes, No
Hypotension requiring treatment	Yes, No
Pulmonary vascular congestion	Yes, No
Bronchospasm	Yes, No
Anaphylactoid (circulatory collapse)	Yes, No
Ventricular fibrillation	Yes, No
Death	Yes, No
Procedural outcome	
Abbreviated because of complication?	Yes, No
Abbreviated because of concern of possible complication?	Yes, No
If abbreviated, were data adequate?	Yes, No

BUN = blood urea nitrogen; NYHA = New York Heart Association.

4,571) because of an actual reaction. The angiographic data obtained were judged to be inadequate in 39 (0.8%) procedures.

Procedure conduct and cardiac disease severity:

We also looked for evidence that study conduct was influenced by the severity of the patient's cardiac disease. This analysis (Table V) shows that angiographers administered smaller volumes of contrast agent to the more severely ill patients. The mean volume for the New York Heart Association class IV patients is significantly smaller than for New York Heart Association classes I, II and III, and still smaller for class V patients. We found similar but less striking relations for left ventricular end-diastolic pressure and cardiac index. The left main disease subgroup also received a substantially smaller mean contrast agent volume.

DISCUSSION

We performed this study to characterize the frequency of clinically important adverse reactions to

TABLE III Characteristics of the Patient Population

	Pts with Data (%)		Mean \pm SD
Demographic			
Age (yrs)	4,630		58.9 \pm 11.3
Gender (% male)	4,630		65.0%
Clinical			
NYHA class			
I	610	(14)	
II	1,300	(30)	
III	1,373	(32)	
IV	946	(22)	
V	85	(2)	
No data	316		
Diabetes mellitus			
No	3,772	(83)	
Yes	767	(17)	
No data	91		
Previous contrast agent reaction			
None	4,250	(94)	
Possible	98	(2)	
Definite	200	(4)	
No data	82		
Corticosteroid prep			
Yes	309	(7)	
No	4,250	(93)	
No data	71		
BUN	4,365		18.5 \pm 9.6
Hemodynamic			
Cardiac index (liters/min/m ²)			
≤ 2.5	519	(26)	
> 2.5	1,498	(74)	
No data	2,613		
Left ventricular end-diastolic pressure (mm Hg)			
< 16	2,014	(49)	
16-25	1,578	(38)	
> 25	521	(13)	
No data	517		
Angiographic			
Contrast agent volume (ml)			
	4,447		143.2 \pm 55.0
No. of diseased coronary arteries			
0	895	(20)	
1	950	(22)	
2	1,043	(24)	
3	1,287	(29)	
Left main	199	(5)	
No data	256		
Estimated ejection fraction (%)			
< 35	51	(8)	
35 to 50	239	(38)	
> 50	346	(54)	
No data	3,994		

SD = standard deviation; other abbreviations as in Table II.

SD = standard deviation; other abbreviations as in Table II.

HOCAs and to provide a framework for assessing the relative roles of HOCAs and LOCAs in cardiac angiography. Our data indicate that a patient population with a large prevalence of severe cardiac disease can safely undergo cardiac angiography using an HOCA. There were no deaths in 4,630 procedures and all major adverse reactions were managed successfully without sequelae. In fact, the 1.3% frequency of major reactions overrepresents the frequency of truly serious events. Half of these reactions were alterations in systemic arterial pressure that responded to treatment.

The adverse reaction rate in our data is comparable to those reported by Lasser,¹³ Shehadi¹⁴ and their co-

workers. Lasser et al,¹² in a study of adverse reactions to intravenously administered HOCAs, reported a 0.52% frequency of class III (severe) reactions and a 2.1% frequency of reactions requiring treatment in patients not pretreated with corticosteroids. They noted a significant reduction in adverse reaction rate in steroid-pretreated patients. Only 6.8% of the patients in our study were steroid pretreated. If Lasser's findings also apply to cardiac angiography, universal corticosteroid pretreatment might achieve a further reduction in the frequency of adverse reactions to HOCAs.

The low adverse reaction rate achieved with HOCAs in this study is noteworthy because most criteria that define groups at high risk include the presence of heart disease.¹⁵⁻¹⁷ Our data cannot be explained by the exclusion of high risk patients because the procedures in this data base were performed before LOCAs were available. The prevalence and severity of cardiac disease were not reported in the Lasser and Shehadi studies, but it is reasonable to presume that our patient population has a greater prevalence of severe cardiac disease than a population undergoing noncardiac radiologic procedures.

The safety record documented by our data appears to be attributable in part to decisions about procedure conduct made by the angiographers. The more seriously ill patients received smaller volumes of contrast agent. Angiographers abbreviated 6.1% of the procedures either because of an adverse reaction or because of concern that a reaction might occur if more contrast agent were administered. It is likely that more reactions would have occurred if these procedures had not been abbreviated. However, the consequence of procedure abbreviation was a 0.8% frequency of failure to obtain adequate diagnostic data—a very undesirable event. This suggests that LOCAs, which would be expected to be better tolerated, might enable precariously ill patients to tolerate a greater contrast agent volume, thus reducing the frequency of inadequate studies.

It is well established that the LOCAs cause less hemodynamic and cardiac electrophysiologic disturbance

than HOCAs.^{8-10,18-20} Consequently, it is possible that LOCAs might cause fewer severe adverse reactions than HOCAs. In fact, if they were not considerably more expensive than HOCAs, LOCAs would probably be universally adopted as the contrast agents of choice for cardiac angiography. The price disparity poses a dilemma to the health care system and to physicians making choices for individual patients.²¹ It is estimated that 866,000 cardiac angiographic procedures were performed in the United States in 1987.²² With the current 15-fold difference in cost, the universal use of LOCAs for cardiac angiography would increase the annual contrast agent expense to the United States health care system by \$100,000,000 over the cost of the universal use of HOCAs. Jacobson and Rosenquist²³ estimate that the universal use of LOCAs for all radiologic procedures that use intravascular contrast agents would cost the United States health care system more than \$1 billion per year.

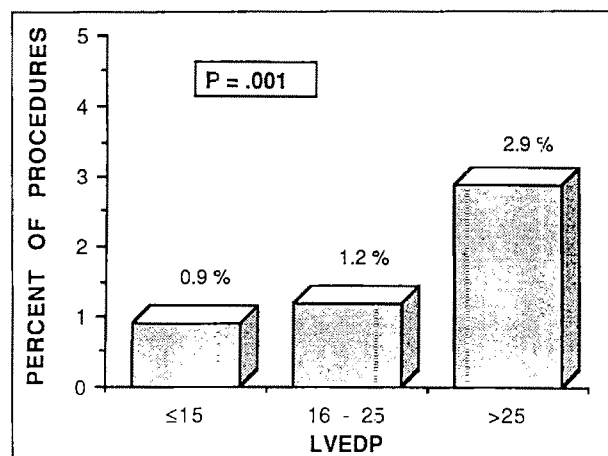


FIGURE 4. Relation between left ventricular end-diastolic pressure (LVEDP) and the frequency of major adverse reactions.

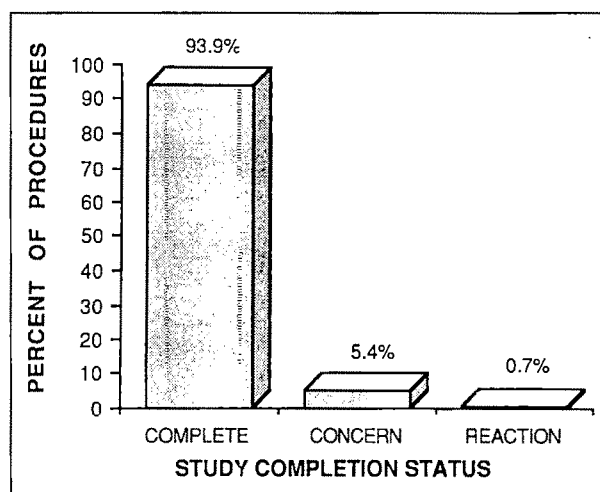


FIGURE 5. Frequency of procedure abbreviation because of either concern that a contrast agent-related adverse reaction might occur (CONCERN), or because of an actual reaction (REACTION). COMPLETE = procedures not abbreviated.

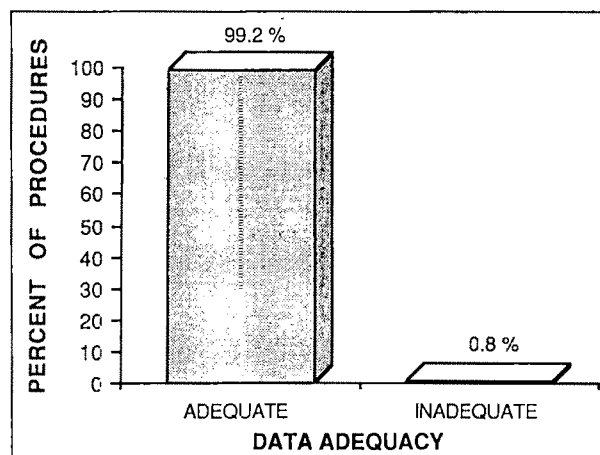


FIGURE 6. Frequency of inadequate data acquisition because of procedure abbreviation (INADEQUATE). ADEQUATE = those procedures in which the data were considered adequate for clinical decision making.

TABLE IV Relation Between Selected Variables and Major Adverse Reaction Frequency

Variable	No. of Events	Percent	95% Confidence Interval
NYHA functional class (p = 0.015)*			
I	3/610	0.5%	0%–1.1%
II	14/1300	1.1%	0.5%–1.7%
III	13/1373	1.3%	0.7%–1.9%
IV	21/946	2.4%	1.3%–3.3%
V	3/85	3.6%	0%–7.7%
Left ventricular end-diastolic pressure (mm Hg) (p = 0.001)			
<16	13/2014	0.9%	0.5%–1.3%
16–25	13/1578	1.2%	0.7%–1.7%
>25	15/521	2.9%	1.4%–4.4%
Left ventricular ejection fraction: (p = 0.141)			
>0.50	4/346	1.2%	0.1%–2.3%
0.35 to 0.50	3/239	3.4%	1.2%–5.6%
<0.35	2/51	3.9%	0%–9.2%
Cardiac index (liters/min/m ²) (p = 0.997)			
≤2.5	3/519	1.5%	0.4%–2.0%
>2.5	25/1498	1.7%	1.0%–2.4%
Extent of coronary artery disease (no. of vessels): (p = 0.657)			
0	10/895	1.1%	0.4%–1.8%
1	11/950	1.2%	0.5%–1.9%
2	15/1043	1.5%	0.8%–2.2%
3	13/1287	1.0%	0.6%–1.5%
Left main	4/199	2.0%	0.1%–3.9%
Previous contrast agent reaction (p = 0.039)			
None	51/4250	1.2%	0.9%–1.5%
Possible	4/98	4.1%	0.2%–8.0%
Definite	2/200	1.0%	0%–3.4%
Contrast agent volume (ml) (p = 0.946)			
<125	22/1677	1.3%	0.8%–1.8%
≥125	37/2770	1.3%	0.7%–1.7%

*p values calculated by chi-square analysis with the appropriate number of degrees of freedom.

Several approaches to this financial dilemma have been proposed. One approach argues that LOCAs should be used universally because the medical and legal costs of the incremental adverse reactions related to universal HOCA use exceed the incremental cost of universal LOCA use.²⁴ Other approaches suggest that LOCAs should be used for certain groups of "high risk" patients.²⁵ Our data demonstrate greater adverse reaction rates in patients with more severe and unstable cardiac disease. However, to date, no objective criteria have been formulated for separating "high risk" patients from "acceptable risk" patients. Thus, at the present time, the angiographer has no clear-cut clinical guidelines for contrast agent selection.^{26,27}

Resolution of this dilemma requires a quantitative assessment of the additional safety and efficacy afforded by LOCAs and the assignment of a value to the improved performance.²⁵ While our data do not answer the question adequately, they do provide a quantitative estimate of the frequency and consequences of reactions to HOCAs in cardiac angiography.

However, the comparative efficacy of LOCAs and HOCAs in enabling angiographers to obtain adequate diagnostic data safely has not as yet been rigorously examined. It is necessary to know whether LOCAs actually perform better, and, if so, whether their benefit exists for all patients or only for "high risk" patients. If the benefit is confined to a subset of patients, it is necessary

TABLE V Relation Between Selected Variables and Contrast Agent Volume

	Mean Volume (ml)	SD	SEM
NYHA functional class (p = 0.001)			
I	143	52	2.1
II	146	52	1.5
III	148	55	1.5
IV	132	60	2.0
V	116	58	6.4
Left ventricular end-diastolic pressure (mm Hg) (p = 0.001)			
<16	145	50	1.1
16–25	144	54	1.4
>25	134	58	2.6
Cardiac index (liters/min/m ²) (p = 0.010)			
>2.5	142	53	1.4
≤2.5	134	56	2.5
No. of diseased coronary vessels (p < 0.001)			
0	139	50	1.7
1	149	59	1.9
2	148	56	1.8
3	142	54	1.5
Left main	125	59	4.3

SD = standard deviation; SEM = standard error of the mean.

to know what characteristics identify it. With such information, a rational approach could be developed for selecting the most appropriate contrast agent for a particular patient.

A prospective trial would be required to obtain these data. In the interim, our data suggest that HOCAs should continue to be the agents of choice for most cardiac angiographic procedures and that LOCAs should be reserved for patients who are severely ill and hemodynamically precarious.

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APPENDIX

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Self-Efficacy and In-Patient Cardiac Rehabilitation

Neil B. Oldridge, PhD, and Barbara L. Rogowski, MS

Self-efficacy reflects an individual's perceptions or beliefs about how capable he or she is of performing a specific activity or task and measures self-confidence to perform that specific activity or task. This study investigated the effect of in-patient cardiac rehabilitation on self-efficacy scores for 3 categories of activities: routine physical activities, daily living tasks and levels of concentration and ability to cope. On discharge from the intensive or coronary care unit, patients without contraindications to early ambulation were randomized to either a ward ambulation program (n = 26) or a dedicated exercise center program (n = 25) with all patients receiving the same standardized education/counseling. There were no differences between the groups in self-efficacy at baseline, at hospital discharge or 7 days later. Significant improvements in self-efficacy scores were observed by day 28 in both groups for routine physical activities and daily living tasks with no change in self-efficacy scores for concentration or ability to cope. At that time the exercise center patients had higher self-efficacy scores for walking time ($p = 0.041$) and overall exertion ($p = 0.024$) than the ward ambulation patients. For the majority of the self-efficacy variables considered, both in-patient exercise rehabilitation programs were equally effective in improving self-efficacy scores for physical activities and daily living tasks over the first 28 days after return to home. The lower cost associated with ward ambulation programs suggests that they are more cost-effective than developing a program in a dedicated in-patient exercise center.

(Am J Cardiol 1990;66:362-365)

As an adjunct to conventional medical and surgical treatment after an acute cardiovascular event, the rehabilitation process is optimally initiated while the patient is still in the hospital. The major components of an in-patient cardiac rehabilitation program—education/counseling and early ambulation—are designed to enhance patients' efforts to regain as normal, productive and active a lifestyle as possible on return to home. Bandura¹ argues that perceived self-efficacy, or an individual's perception or belief about his capability to actually perform a specific behavior or task, influences the acquisition of new behaviors as well as the resumption or inhibition of prior behaviors. The usefulness of self-efficacy in measuring patients' perceptions about various physical activities and assessing improvement as a result of various interventions has been demonstrated in cardiac patients.²⁻⁶

In-patient education/counseling programs provide information that prepares the patient to deal with the resumption of normal daily activities with less anxiety on return to home.⁷⁻⁹ Although neither significant beneficial nor deleterious physiologic effects of in-patient exercise rehabilitation before discharge from hospital have been demonstrated,¹⁰ early ambulation programs have become routine clinical practice for cardiac patients without medical complications; these programs may be administered on the ward or in a specifically designated exercise center located off the ward. Another goal of exercise rehabilitation while still in the hospital is to prevent deleterious psychological effects. It has been argued that participation in an in-patient exercise therapy program increases patients' self-confidence.¹¹ Presumably, the justification for the added space and equipment requirements, staff and other budgetary considerations associated with an in-patient exercise center is that it provides physiological and psychological benefits that a ward program does not. There is, however, little empirical evidence of the behavioral benefits of an in-patient exercise center compared to a ward ambulation program after an acute cardiovascular event. The present study investigates the effects of a standardized education/counseling program in combination with 2 different in-patient exercise rehabilitation programs using self-efficacy as the outcome measure of interest.

METHODS

At this institution, cardiac patients with no contraindications to early ambulation are routinely referred to the in-patient cardiac rehabilitation on discharge from either the coronary care or intensive care units. On the day of discharge from the unit, the rehabilitation nurse

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TABLE I Clinical, Physical and Demographic Variables

	Total Group (n = 76)	Completed (n = 51)	Not Completed (n = 25)
Age (yrs)	59.0 ± 11.2	56.9 ± 11.1	65.1 ± 9.6*
Weight (kg)	79.2 ± 13.0	79.8 ± 13.8	77.7 ± 11.3
Height (cm)	172 ± 9	172 ± 10	173 ± 8
Ejection fraction (%)	56 ± 14	55 ± 14	56 ± 14
Gender (%)			
Male	76	75	80
Female	23	25	20
Race (%)			
White	88	92	80
Black	9	6	16
Other	3	2	4
Referral reason (%)			
MI†	20	16	24
CABG	63	68	64
Other	17	16	12
Smoking status (%)			
Never	22	18	30
Past	57	59	52
Current	21	23	18
Job status (%)			
Employed	49	53	40
Unemployed	10	10	12
Retired	41	37	48

* p < 0.05, unpaired t test for completed vs not completed).

† With and without bypass surgery.

CABG = coronary artery bypass grafting; MI = myocardial infarction.

TABLE II Self-Efficacy Scores for Physical Activities on Discharge from the Intensive or Coronary Care Unit (Base), on Discharge from Hospital (Discharge), 7 and 28 Days Later for Patients Randomized to Ward Ambulation or the Exercise Center

	Time	Ward Ambulation (n = 26)	Exercise Center (n = 25)	p Value*
Exertion	Base	60	61	NS
	Discharge	60	59	NS
	7 days	54	60	NS
	28 days	64	76†	0.024
Stairs	Base	40	44	NS
	Discharge	47	44	NS
	7 days	60	65	NS
	28 days	76†	83†	NS
Lifting	Base	45	57	NS
	Discharge	49	59	NS
	7 days	52	55	NS
	28 days	66†	73†	NS
Walk distance	Base	67	69	NS
	Discharge	73	78	NS
	7 days	76	83	NS
	28 days	91†	97†	NS
Walk time	Base	62	71	NS
	Discharge	73	81	NS
	7 days	82	88	NS
	28 days	91†	99†	0.041

* One-factor analysis of variance for differences between ward ambulation vs exercise center at each time.

† p < 0.005 by repeated measures analysis of variance.

explained that the purpose of the study was to investigate the effectiveness of 2 different in-patient exercise rehabilitation programs and that it had been approved by the Institution's Review Board. The research associate administered the self-efficacy questionnaire to the patient immediately after agreement for randomization was obtained. The questionnaire was repeated on the day of hospital discharge and at that time the patient was given 2 differently colored questionnaires for use on days 7 and 28 after discharge; on those days, the research associate administered the appropriate questionnaire over the telephone.

Standardized education/counseling was offered to all patients. Mobilization for all patients began with progressive active/resistive exercise for upper and lower extremities. Ambulation progressed until the patient could tolerate 800 feet; then the randomized patients started their allocated program.

Ward ambulation: The duration of supervised and telemetered walking was gradually increased as tolerated with intensity limited to a heart rate of ≤20 beats/min above resting or a rating of perceived exertion of 3 to 4 on the ratio scale. There were daily supervised sessions and, with no contraindications from the previous session, patients were encouraged to ambulate on their own on the ward.¹²

Exercise center: Similar exercise prescription intensity limitations were used in the exercise center; patients exercised daily on the treadmill or on the cycle ergometer under supervision and while monitored. The initial duration on the treadmill was 2 × 5 minutes with a speed of 1 mph with most patients walking for 20 to 25

minutes at a speed of 2 mph by the time of discharge; cycle duration was 5 minutes at the appropriate heart rate and perception of exertion. Exercise center patients were encouraged to walk on the ward unless there were contraindications on the previous exercise session.¹²

Patient characteristics and outcome measures: On discharge from the coronary or intensive care units, reason for referral to the rehabilitation program was noted and ejection fraction was measured; the latter was used to stratify and then randomize patients. Entry physical characteristics and demographic data included gender, age, weight, height, race, smoking and occupational status. On day 28, data on return to work, outpatient rehabilitation and exercise habits since discharge were collected.

Self-efficacy: Self-efficacy scales were developed to measure patients' self-perceived ability to carry out the following physical activities: walking distance, walking time, climbing stairs, lifting objects and overall ability to tolerate physical exertion.^{2,3} We developed self-efficacy scales for the estimation of the ability to carry out usual household and daily activities, to drive a vehicle, to return to work, to cope with stress and to concentrate. Self-efficacy for any given task was the sum of the self-efficacy estimates for progressive levels of the task divided by the number of levels for that task.^{2,3} Self-efficacy was measured on the day of discharge from the coronary or intensive care unit, at discharge from hospital and 7 and 28 days later.

Statistical analyses: Self-efficacy data were compared using 1-way analysis of variance for testing differ-

TABLE III Self-Efficacy Scores for Daily Living Tasks and Mental Activities on Discharge from the Intensive or Coronary Care Unit (Base), or Discharge from Hospital (Discharge), 7 and 28 Days Later for Patients Randomized to Ward Ambulation or the Exercise Center

	Time	Ward Ambulation (n = 26)	Exercise Center (n = 25)	p Value*
Daily living tasks				
Household activities	Base	84	86	NS
	Discharge	85	90	NS
	7 days	89	87	NS
	28 days	93 [†]	96 [†]	NS
Daily activities	Base	76	78	NS
	Discharge	76	75	NS
	7 days	77	80	NS
	28 days	86 [†]	87 [†]	NS
Driving	Base	82	91	NS
	Discharge	83	88	NS
	7 days	88	91	NS
	28 days	95	98	NS
Return to work	Base	43	69	NS
	Discharge	43	69	NS
	7 days	46	64	NS
	28 days	64 [†]	77 [†]	NS
Mental activities				
Stress	Base	82	87	NS
	Discharge	85	80	NS
	7 days	85	87	NS
	28 days	87	91	NS
Concentration	Base	92	92	NS
	Discharge	96	93	NS
	7 days	96	88	NS
	28 days	96	97	NS

* One-factor analysis of variance for differences between ward ambulation vs exercise center at each time.

[†] p < 0.05; [‡] p < 0.005 by repeated measures analysis of variance.

ences between the groups at any given time and repeated measures analysis of variance for change in self-efficacy scores in the randomized patients.

RESULTS

Agreement for randomization was sought from 76 consecutive patients referred to in-patient cardiac rehabilitation on the day of discharge from either the coronary or intensive care unit. Of the 64 who agreed to randomization, 13 dropped out of the study before it was completed. Physical characteristics, ejection fraction, reason for referral, smoking status and occupational status of the total group (n = 76), those who completed the study (n = 51) and the 25 who did not (including randomization refusals) were similar except for the older age observed among the latter patients; there were no significant differences between the patients randomized to either the ward program (n = 26) or the exercise center (n = 25) (Table I). There were no differences in the number of days on which exercise rehabilitation was possible after discharge from the coronary or intensive care unit with a mean of 1.9 actual treatment days before discharge from hospital (excluding the day of discharge from the unit, days to achievement of 800-foot ambulation and the day of hospital discharge). The mean time to hospital discharge was 7.2 days.

There were no significant differences in any of the self-efficacy scores between the 2 groups of patients on entry into the study (Table II). There were no differences in any of the self-efficacy scales at discharge or 7 days later (Tables I and III). By day 28 after discharge, only walking time (p < 0.041) and exertion (p < 0.024) self-efficacy scores were higher among the exercise center patients than the ward ambulation patients (Table II). In both groups of patients, repeated measures analysis of variance demonstrated significant improvements (p < 0.005) in self-efficacy scores over the duration of the study for all physical activities (Table II), for household activities (p < 0.05), for each of the other daily living tasks (p < 0.005) and for return to work (p < 0.005 for ward ambulation, p < 0.05 for exercise center) but no improvement in self-efficacy for mental activity (Table III). It is clear from Table III that most of the improvement in self-efficacy occurred between days 7 and 28 after discharge. There were no significant interaction terms.

By the end of the trial, 5 of the 27 previously employed subjects had returned to work; 1 of 15 in the ward group had returned compared to 4 of 12 in the exercise center group (p = 0.064). There were no differences in the number of patients participating in a supervised rehabilitation program by day 28 (ward = 6 of 26; exercise center = 7 of 25) or in the numbers reporting regular exercise (ward = 25 of 26; exercise center = 24 of 25). No patient reported any untoward side effects associated with exercising at home.

DISCUSSION

With the introduction of improved technologies and the incorporation of the Diagnostically Related Group payment system, the hospital stay after myocardial infarction has been reduced from ≥ 3 weeks in the mid-1960s¹³ to as short as 3 days for patients without complications in the late 1980s.¹⁴ With a mean time to discharge in this study of 7.2 days, and 2 to 4 days in the intensive or critical care units, a decreased hospital stay is not a reasonable measure of the effectiveness of in-patient cardiac rehabilitation. Siva-ajan et al¹⁰ point out that, with earlier hospital discharge after an acute cardiovascular event, attempts at earlier rehabilitation must reach a point of diminishing physiologic benefits. This also appears to be true for behavioral benefits. We have demonstrated that self-efficacy scores in both groups changed little before hospital discharge. However, by day 28 after discharge, self-efficacy scores for performing most of the physical activities and daily living tasks had improved similarly and significantly in both in-patient exercise groups. This raises the possibility that the observed improvement in self-efficacy might be largely associated with the resumption of usual daily activities after discharge, which, in turn, raises the question of whether or not in-patient exercise programs are warranted.

In-patient exercise rehabilitation programs may be appreciated by patients^{10,15} but they may not be effective. These programs can be run in sophisticated centers

requiring considerable space, using expensive ergometers and other exercise equipment and necessitating the use of dedicated telemetry systems with supervision by trained personnel. Alternatively, programs supervised by trained personnel can also be run without exercise equipment on the ward, using existing ward telemetry equipment. The similar improvements seen in most self-efficacy variables 28 days after hospital discharge in patients randomized to both rehabilitation programs suggest that ward ambulation programs would be more cost-effective than an exercise program run in a dedicated center.

Although we observed a higher rate of return to work by day 28 among the exercise center patients, who also had marginally higher self-efficacy scores for return to work at both baseline and discharge, the small numbers in this study do not permit any definitive conclusions about return to work. However, the trend may have important implications as there have been recent reports that, after coronary angioplasty,¹⁶ patients with high self-efficacy scores for return to work did, in fact, resume work sooner than those with low self-efficacy. In addition, early hospital discharge after myocardial infarction has also recently been associated with an earlier return to work, although self-efficacy was not measured in that study.¹⁴

While improved cardiovascular risk factors,¹⁷ a greater exercise tolerance¹⁸ and a reduced mortality¹⁹ have been associated with outpatient cardiac rehabilitation, early mobilization after myocardial infarction has little positive or negative effect on 10-year mortality²⁰ and in-patient exercise therapy has not demonstrated either beneficial or deleterious short- or long-term physiologic effects.¹⁰ Based on the results of this trial, our conclusions are that the differences in the self-efficacy scores—observed only for walk time and overall exertion—do not warrant the added costs associated with a dedicated in-patient exercise center. However, the various clinical benefits of early ambulation,¹¹ including the improved self-efficacy scores seen in this trial 28 days after discharge, appear to warrant the use of prescribed in-patient ward ambulation for appropriately selected patients.

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The Hazards of Using Type 1C Antiarrhythmic Drugs for the Treatment of Paroxysmal Atrial Fibrillation

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There have been several favorable reports of the efficacy of the class 1C drugs, flecainide, encainide and propafenone, in preventing recurrences of paroxysmal atrial fibrillation, an arrhythmia that can be troublesome, and in some patients, incapacitating. Because these drugs have an excellent noncardiac side-effect profile, physicians may be tempted to use these drugs for the treatment of paroxysmal atrial fibrillation refractory to class 1A drugs such as quinidine, procainamide or disopyramide. The article in this journal by Feld et al¹ documents the appearance of a rapid ventricular response in patients treated with encainide or flecainide for refractory atrial fibrillation/flutter and the new appearance of atrial arrhythmias with a rapid ventricular response in patients treated with these drugs for nonsustained ventricular tachycardia or for incessant ventricular tachycardia. Two patients had serious complications associated with the onset of atrial arrhythmias; 1 developed hypotension with a systolic blood pressure of 70 mm Hg and the other had a non-Q-wave infarction. These complications were observed in 6 of 60 patients (10%) receiving encainide or flecainide over a 12-month period. Murdock et al² found that 4 of 82 (5%) patients receiving propafenone developed a wide QRS complex associated with atrial flutter. Two of these patients had 1:1 conduction at rates of 200 and 275 beats/min. Of particular note is that these same investigators did not observe these adverse effects during early follow-up of 1 to 24 months (mean 5 ± 6).³ Wide complex tachycardia also has been seen in 7 of 209 patients treated for paroxysmal atrial fibrillation with recainam, a class I drug with 1C properties (de Vane P, Wyeth-Ayerst Pharmaceutical Co.). These adverse cardiac effects should alert physicians to the risks of using this class of drugs for the treatment of paroxysmal atrial fibrillation or flutter. The rapid ventricular response to atrial fibrillation can be explained by the electrophysiologic effects of class 1C drugs. They act primarily on the fast sodium channels of cardiac tissue, they depress the rate of depolarization of phase 0 of the action potential and they slow conduction in the atrium, in the atrioventricular node and in the ventricle.

On the other hand, they have little effect on anterograde refractoriness of the atrioventricular node. Changes seen on the electrocardiogram are prolongation of the PR interval and QRS duration. It should be emphasized that PR prolongation does not exclude the possibility of rapid conduction through the atrioventricular node. Except in Wenckebach and higher grades of atrioventricular block, slowing of conduction in the atrioventricular node has little influence on the number of impulses per unit time that can be transmitted through the atrioventricular node.⁴ This was well understood by Mendez and Mendez⁴ nearly 40 years ago. They wrote, "A decrease in speed of conduction (in the atrioventricular propagation system) however, could result in a greater shift of phase between the ventricular impulses and the auricular impulses which originate there. That is, if the auricle of a mammalian heart beats at the highest rate that the ventricle can follow, a decrease of speed of conducted impulses in the auriculo-ventricular propagation system could result only in an increase of the P-R interval and not in a decrease in the ventricular rate."⁴ They also stated that the functional refractory period of the atrioventricular propagating system limits the maximal rate at which the ventricle can respond to the auricle. The 1C class of antiarrhythmic drugs decreases atrioventricular conduction but has little effect on refractoriness of the atrioventricular node. The dissociation of conduction and refractoriness has been seen in the dog after radiofrequency catheter ablation of approaches to the atrioventricular node.⁵ It is possible that the 1C drugs affect cells in this region, but not those located more distally in the atrioventricular node that are primarily responsible for the refractory properties of the atrioventricular node.

The sequence that results in the rapid ventricular response in atrial fibrillation/flutter under the influence of type 1C drugs may be the following: the atrial rate during atrial fibrillation is slowed due to a drug-induced decrease in the speed of atrial conduction. With slowing, the atrial rhythm may regularize to atrial flutter. The combination of these 2 effects, that is, slowing of the atrial rate and regularization, results in fewer impulses partially penetrating the atrioventricular node. This results in decreased refractoriness of the atrioventricular node. If the atrial rate is slowed sufficiently, the atrioventricular node may permit 1:1 atrioventricular conduction. With the onset of rate-related hypotension, there is increased adrenergic effect, further facilitating rapid atrioventricular nodal conduction. With a rapid

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ventricular response, the QRS complex is observed to widen. The wide complex QRS is due to the fact that these drugs exhibit frequency dependence. That is, with an increase in the rate of stimulation, there is enhanced blockade of the fast-channel sodium current, causing further slowing of impulse propagation. The clinical manifestation of this phenomenon is a rapid, wide QRS tachycardia that may be indistinguishable from ventricular tachycardia. For patients on class 1C therapy, the QRS duration during regular tachycardia is directly related to the rate of the tachycardia and is significantly longer than in patients treated with other antiarrhythmic drugs.⁶

These adverse cardiac effects are not unique to the type 1C drugs. It is well recognized that digitalis should be given before attempting clinical cardioversion with quinidine. This latter drug slows atrial conduction and enhances atrioventricular nodal conduction by its vagolytic effect. However, the type 1C drugs are extremely potent in slowing atrial conduction and, as previously stated, have little effect on anterograde atrioventricular nodal refractoriness. Therefore, this potentially serious adverse cardiac effect should be more commonly observed with the type 1C drugs. Another characteristic of the type 1C antiarrhythmic drugs is that they have significant negative inotropic effects. Thus, the hemodynamic effects of a rapid ventricular response may not be well tolerated. It may be hypothesized that the frequency dependence manifested as widening of the QRS complex may also apply to its negative inotropic effects so that the negative inotropic effects are intensified at increasing rates.

At the present time, we do not know how to identify patients with paroxysmal atrial fibrillation who may develop the above complication. It is not limited to patients with known organic heart disease. Personally, I have observed this effect in 2 patients who are "lone fibrillators" without underlying heart disease. Also, it is not known whether short-term drug testing with a type 1C drug with initiation of atrial fibrillation by intracardiac or esophageal pacing will identify patients at risk

for development of a rapid ventricular response. The rapid response to atrial fibrillation may not be seen for weeks or months despite earlier recurrences of atrial fibrillation without this rapid ventricular rate.⁵ This makes one pessimistic that predicting this rapid ventricular response in an individual patient could be achieved by short-term drug testing.

Currently, it seems advisable to restrict the use of class 1C drugs for treatment of paroxysmal atrial fibrillation refractory to type 1A antiarrhythmic drugs and to use β -blocking drugs⁷ or calcium-channel blocking drugs such as verapamil or diltiazem concomitantly with digitalis when treating paroxysmal fibrillation with type 1C drugs. The dose of digitalis should be adjusted so that it is in the therapeutic range of 1 to 2 ng/ml. It is likely, but not yet certain, that concomitant administration of these drugs to increase atrioventricular nodal refractoriness will prevent the rapid ventricular response.

The possibility of ventricular proarrhythmia in patients receiving type 1C drugs has also been well documented⁸ and is an additional reason for caution in prescribing type 1C drugs for the treatment of paroxysmal atrial fibrillation.

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Rationale Against the Drug Treatment of Marginal Diastolic Systemic Hypertension

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The Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure¹ does not recommend drug treatment for uncomplicated hypertension when the diastolic blood pressure (BP) is in the range of 90 to 94 mm Hg (marginal hypertension). They advise instead nonpharmaceutical therapy with periodic examinations to detect possible progression of hypertension. Most physicians, however, still use 90 mm Hg as the level at which they will begin treatment with drugs if necessary and at least 2 authorities^{2,3} emphasize the importance of decreasing EP using drug treatment when needed in all hypertensive patients, including those with diastolic levels as low as 90 mm Hg. This report will review some of the background data concerning the effectiveness of treatment of patients with diastolic BP in the range of 90 to 94 mm Hg. The question is of considerable importance because patients with diastolic BP in this marginal range comprise approximately 40% of the hypertensive population.^{4,5}

Level of diastolic blood pressure and coronary heart disease mortality: The leading cause of death in marginal hypertension is coronary heart disease, which is 3 times greater than stroke, the second leading cause. However, cardiovascular risk is lower in marginal hypertensive patients compared to patients with higher levels of diastolic BP.⁶

The curve relating diastolic BP and coronary heart disease mortality increases steeply at levels above 100 mm Hg.⁶ Anderson,⁷ using 1978 data from the Framingham study, pointed out that the curve flattened out at diastolic BP levels between 70 and 90 mm Hg; that is, there was no increase in coronary heart disease mortality between 70 and 90 mm Hg. No such inflection or "dogleg" in the curve was seen with respect to systolic BP where coronary heart disease mortality increased continuously from the lowest levels. This inflection in the diastolic curve was not recognized before because of the previous practice of drawing a smooth linear regression curve, which will never disclose a dogleg. This author has been informed by Dr. A. D'Agostino of the Framingham study that their most recent, still unpublished data also show a dogleg or J-shaped diastolic curve. Furthermore, 4 other epidemiologic studies⁸ also show in the unsmoothed curves relating diastolic BP

and coronary disease mortality an inflection in the range of 95 to 105 mm Hg diastolic BP (Figure 1). The relatively flat portion of the dogleg in all of the studies included the range of marginal hypertension, suggesting that the risk of coronary heart disease is no greater in marginal hypertensive patients than in the normotensive population.

Evidence for a dogleg or even J-shaped curve also has been reported for treated hypertensive patients. The inflection occurs at approximately 90 mm Hg with an increasing incidence of coronary heart disease deaths at progressively lower levels of diastolic BP.^{9,10} Cruickshank¹⁰ reported that this phenomenon occurred only in patients with evidence of preexisting ischemic heart disease. He suggests that in patients with narrowed coronary arteries, myocardial perfusion, which occurs mainly in diastole, may become critical at a diastolic BP of approximately 85 mm Hg.¹⁰ Other groups, however, have noted a J-shaped curve¹¹⁻¹³ in the absence of clinically evident coronary heart disease. One study in the elderly found a J-shaped curve¹⁴ while another did not.¹⁵

Because the epidemiologic studies described before found J-shaped or dogleg curves, it is not surprising that the same phenomenon is seen when the diastolic BP is decreased to <90 mm Hg by treatment. Although final proof is still lacking, the recent evidence suggests that diastolic BP possibly should not be decreased to <90 mm Hg.

Effect of drug treatment on heart disease mortality in marginal hypertension: Most multiclinic trials (Table I) indicate that antihypertensive drug treatment has not been effective in preventing coronary heart disease morbidity-mortality.¹⁶⁻²²

Opposed to 7 negative trials, only 2 found that treatment was effective in preventing coronary heart disease, the relatively small European Working Party on Hypertension in the Elderly Trial¹⁵ and the Hypertension Detection and Follow-up Program.²³ However, the latter was not a controlled trial in the accepted sense because the general care of the control group was quite different from that of the treatment group.

The 2 most definitive trials from the point of view of adequate numbers and appropriate design were the Australian¹⁶ and Medical Research Council¹⁹ (MRC) trials. Their overall results indicated no significant protection against major coronary heart disease events from the use of antihypertensive drugs. These negative results are supported by the 5 remaining trials listed in Table I.^{17,18,20-22}

Effect of drug treatment on stroke prevention: It is generally agreed that antihypertensive therapy decreases stroke morbidity and mortality.

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TABLE I Effect of Treatment on Major Coronary Heart Disease Events: Summary of Trials

Trial	No. of Subjects	Entry DBP (mm Hg)	Incidence CHD Events		% Difference
			Treatment	Control	
Showing no or negative benefit					
VA	380	90 to 114	11	13	13
USPHS	389	90 to 115	7	6	-17
Oslo	785	90 to 109	20	13	-54
Australian	3,427	95 to 109	33	33	0*
MRFIT	7,012	90+	115	124	5
MPPCDM	1,222	95+	19	9	-111
MRC	17,354	90 to 109	222	234	12
Showing benefit					
EWPHS	840	90 to 119	7	16	56
HDFP	7,825	90 to 104	86	107	20

Includes either mortality alone or morbidity plus mortality when data for both are given.

* Intention to treat.

CHD = coronary heart disease; DBP = diastolic blood pressure; EWPHS = European Working Party High Blood Pressure in the Elderly; HDFP = Hypertension Detection and Follow-up Program; MPPCDM = Multifactorial Primary Prevention of Cardiovascular Diseases in Middle-Aged Men; MRC = Medical Research Council; MRFIT = Multiple Risk Factor Intervention Trial; USPHS = United States Public Health Service; VA = Veterans Administration.

In marginal hypertension, however, the risk of stroke is relatively low. The MRC trial¹⁹ found that treatment for 1 year protected against stroke in only 1 in 850 patients with a diastolic BP of 90 to 109 mm Hg. However, in patients with a baseline diastolic BP of 90 to 99 mm Hg, the incidence of stroke was only one-third or less than in the 105 to 109 mm Hg range (Table II). Therefore, the number of milder hypertensive patients required to be under treatment in order to prevent a single stroke must have been considerably >1 in 850. These results further call into question the cost-effectiveness of treatment of marginal hypertensive patients even for the prevention of stroke.

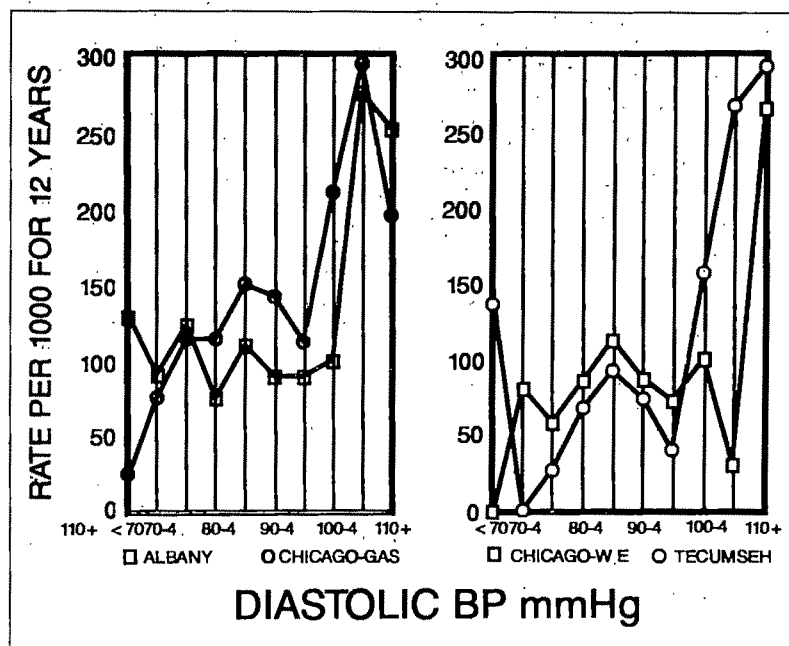
Adverse effects and cost of drug treatment: Although most patients tolerate antihypertensive drugs quite well, moderate to severe adverse effects may occur in a few. In the Veterans Administration trial,²⁴ for example, of 180 actively treated patients, 2 were withdrawn because of presumed toxic reactions, and side effects such as lethargy, weakness and nasal stuffiness

were significantly more frequent in the treated patients as compared to the placebo control subjects. The MRC trial²⁵ reported that in men, adverse effects with bendroflumethiazide or propranolol were significantly increased as compared to placebo.

The cost of lifelong treatment for such a large number of patients is also a major consideration. This cost is magnified by the current trend to prescribe new, quite expensive drugs such as calcium antagonists and converting enzyme inhibitors in place of the less costly, older agents such as generic thiazide diuretics, propranolol and reserpine. Drug treatment for the 20 million marginal hypertensive subjects could total, therefore, several billion dollars per year.

The course of untreated marginal hypertension: In the Australian trial,²⁶ 1,943 placebo-treated patients had diastolic BP for the 3 initial visits averaging between 95 and 109 mm Hg and remaining at ≥ 95 mm Hg at the third visit. The investigators also followed, without active treatment, 325 patients whose diastolic

FIGURE 1. Coronary heart disease death rates/1,000 patient years for 12 years recorded in 4 epidemiologic studies (Albany, Chicago Gas, Chicago Western Electric and Tecumseh) related to diastolic blood pressure (DBP). Graphic representation of tabular data as presented by Cruickshank et al.¹⁰ The 4 curves all showed a dogleg inflection with a relatively flat portion between <70 and ≥ 95 mm Hg DBP. Mortality rates then increased steeply beginning at levels of DBP ≥ 100 mm Hg. DBP, therefore, correlated directly with rates of coronary heart disease only at levels ≥ 100 mm Hg. Mortality rates were no higher in the marginal hypertensive range than in the normal range of DBP.



BP averaged <95 mm Hg during the 3 initial visits. After 3 years, 48% of the total untreated patients had reverted to normal BP without treatment.

Many physicians regard 3 visits as being sufficient to characterize the average BP. The Australian trial indicated that the BP of some patients will require ≥ 4 months to decrease to normal.

None of the patients with initial diastolic BP <95 mm Hg at baseline developed elevation >109 mm Hg over 3 years of follow-up, whereas 94 of the patients exhibiting baseline diastolic BP levels between 105 and 109 mm Hg increased to >109 mm Hg during the trial. Thus, marginal hypertensive subjects rarely exhibit severe acceleration of BP over 3 years, whereas moderately severe hypertensive subjects often do. A lesser increase of 95 to 109 mm Hg occurred in some of the marginal patients (Table III). However, these more moderate increases can be safely managed by 6-month visits when they would be detected and treated before the BP reached a high-risk level.

The placebo group who remained in the range of 90 to 94 mm Hg throughout the trial, that is, the untreated marginal hypertensive subjects, exhibited no significantly greater rate of trial end points than the placebo patients who maintained normotensive levels of diastolic BP of 85 to 89 mm Hg (Table IV). These data further suggest the low risk associated with untreated marginal hypertension. By contrast, in the placebo patients maintaining higher levels of 95 to 99 mm Hg, the event rate per year nearly doubled as compared to the marginal hypertensive subjects and then increased more steeply with a diastolic BP >100 mm Hg. At similar levels of diastolic BP, the treated patients in general had higher rates of trial end points than the placebo patients.

Marginal hypertension combined with systolic hypertension: Systolic hypertension is defined as a systolic BP of 160 mm Hg or higher. Although often associated, there are important differences between systolic and diastolic hypertension.²⁷ The latter is characterized by constriction of arterioles while systolic hypertension results from loss of compliance of the aorta causing a steep systolic increase during cardiac ejection. Diastolic BP may remain normal if the arterioles are not constricted.

Systolic hypertension in the presence of normal or marginal diastolic hypertension often occurs in the aged. Under the stress of the first 1 or 2 medical examinations, these individuals may have an increased cardiac output, resulting in systolic hypertension. This response is amplified by impaired baroreceptor moderation of the BP elevation with aging. During subsequent visits, as elderly patients become accustomed to the clinic environment, the increased cardiac output often moderates and the systolic BP reverts to normal. Systolic hypertension, however, may persist in many other patients.

Epidemiologic studies indicate that systolic hypertension poses as great or greater a risk as diastolic hypertension.²⁸ However, there are presently no data from controlled clinical trials for determining the effectiveness of drug treatment in isolated systolic hypertension. It is, therefore, uncertain whether treatment will be

TABLE II MRC Trial: Stroke Rates/1,000 Patient Years in Relation to Average Entry Diastolic Blood Pressure

Strokes/1,000 Pt Yrs	Average Entry DBP (mm Hg)			
	<95	95 to 99	100 to 104	105 to 109
Active treatment	0.3	1.8	1.4	1.4
Placebo	1.4	2.3	3.1	4.4
Difference				
"Strokes prevented"	1.1	0.5	1.7	3.0

DBP = diastolic blood pressure.
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TABLE III Australian Trial—Placebo Group: Average Diastolic Blood Pressure After 3 Years Compared to Average Diastolic Blood Pressure at Entry

Average DBP After 3 Yrs (mm Hg)	Average DBP First 3 Visits (mm Hg)			
	<95	95 to 99	100 to 104	105 to 109
>109	0	4%	13%	40%
95 to 109	15%	30%	41%	35%
<95	75%	58%	38%	16%

DBP = diastolic blood pressure.
Reproduced from Management Committee of the Australian Therapeutic Trial in Mild Hypertension²⁶ with permission of the publisher.

TABLE IV Data from Australian Trial—Trial End Points: Rates by Average Diastolic Blood Pressure Throughout the Study for Active and Placebo Subjects

Average DBP (mm Hg) Throughout the Trial	TEP Rates/1,000 Yrs	
	Active	Placebo
<85	12.3	11.8
85 to 89	13.4	18.8
90 to 94	29.7	16.2
95 to 99	75.8	28.7
>100	84.5	60.4

DBP = diastolic blood pressure; TEP = trial end points.

beneficial or at what level to begin. Some physicians initiate drug treatment of persistent systolic hypertension on the reasonable but unproven assumption that such treatment will prevent stroke and heart failure, which are both prevalent in aged hypertensive patients.

Conclusions: Few patients with uncomplicated marginal hypertension require drug treatment. However, other hygienic measures such as weight reduction if needed, salt and alcohol restriction, regular exercise, cessation of cigarette smoking and especially dietary restriction of saturated fats and cholesterol are indicated. Also, antihypertensive drug treatment is advisable in marginal hypertensive subjects with diabetes mellitus or with renal impairment from other causes or congestive heart failure or with moderate to severe left ventricular hypertrophy or other evidence of organic changes secondary to hypertension. Aside from these exceptions, most of which are infrequent among marginal hypertensive subjects, there is little evidence that these patients will achieve enough benefit to justify the costs and adverse effects of antihypertensive drug treatment.

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Bird Brains: The Evolution of Scientific Misconduct

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Hardly a week goes by without a new revelation of scientific fraud, plagiarism, or conflict of interest appearing in *Science* or *Nature*, *Newsweek* or *Time*. Is there really an epidemic of immoral investigators out there? Is the pressure to publish and the lack of supervision causing some amoral individuals to bend the rules more often? Or is the issue largely illusory, a result of heightened scrutiny of the moral majority in response to a few notorious transgressions?

In attempts to forestall the threatened epidemic, the National Academy of Science, the American Association for the Advancement of Science, the Council of Biology Editors and the American Bar Association have all held symposia on the ethical conduct of science¹; the Department of Health and Human Services,² the Institute of Medicine,³ and the Association of American Universities⁴ have begun to issue guidelines for ethical conduct; a prominent journal editor has called for a formal audit of the scientific literature⁵; and a member of Congress is considering the introduction of federal legislation.⁶

Is all this activity necessary? To answer this question, I will propose a simple theoretical model for the evolution of scientific misconduct, and will thereby show that well-intentioned efforts to control the epidemic could actually serve to spread it.

The model is based on one first proposed by Maynard Smith to explain the evolution of aggressive behavior in animals,⁷ and my description closely parallels that of Dawkins.⁸ The model assumes that individual members of the population are competitors for some common resource. In nature (the jungle, not the journal) this resource might be the food necessary to one's survival or the sexual partners necessary to the survival of one's genes. In science (again, not the journal) the resource might be the research funds, facilities, publications, and prestige necessary to the survival of one's ideas (including one's ideas about the best way to promote those ideas).

Let us begin with the simplest possible jungle, in which there are only 2 strategies for survival: dove and hawk. Doves engage in long periods of empirical ob-

servation, statistical analysis and intellectual debate. Hawks lie, cheat and steal. Whenever doves meet at the watering hole each evening, they argue in a dignified way about the events of the day, and carefully document their arguments in the jungle book for all to see. Eventually, one dove decides the other is right, the issue is unimportant, or the argument is uninteresting, and politely backs down. No one gets hurt. When hawks meet, on the other hand, they fight ferociously until one of them is severely injured. Whenever a dove meets a hawk, the dove flies away quickly before being hurt.

The survival of one's ideas is the name of this game. Accordingly, we can score the outcome associated with each of these pairings along some arbitrary utility scale representing the likelihood that one's ideas will spread throughout the jungle: 30 points for a win, 0 points for a loss, -10 points for wasting time, and -480 points for being hurt. (These utilities are highly subjective. I have chosen 30 points to represent the modest gain associated with acceptance of one's idea by another, and -480 points to represent the material loss associated with outright exposure as a miscreant, because these values are generally consistent with my own personal beliefs. Readers are invited to experiment with alternative values representing their beliefs.)

Each time a dove meets a dove there will be a long contest resulting in a winner (30 points for the win -10 points for wasting time) and a loser (0 points for the loss -10 points for wasting time). Because each dove will win half the time, the average score for dove/dove encounters is 5 points ($20/2 - 10/2$). In a population made up entirely of doves, each dove ekes out a meager existence.

Suppose now a single hawk enters this idyllic jungle. Because it is the only hawk around, each contest will be with a dove, and it will win every one of these contests without being hurt, giving it an average score of 30 points compared with an average of 5 points for doves. This advantage over the competition will quickly attract other hawks to the jungle, and might even entice some of the less dignified doves to become more aggressive.

As a result, hawks will begin to encounter other hawks. Whenever a hawk meets another hawk, one of them will win (30 points) and the other will be injured (-480 points). Because each hawk has an even chance of winning, the average score for hawk/hawk encounters is -225 points ($30/2 - 480/2$). In a population made up entirely of hawks, each hawk does very poorly.

A dove will not do very well either, but at least it will do better than a hawk. Although the dove will lose every one of its encounters in this savage jungle, its aver-

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age score of 0 is still much better than the hawk's average score of -225. In a population of hawks, therefore, a dove has the advantage. As before, this advantage too will not go unnoticed for long. It will eventually attract more doves, and might convince some of the less malicious hawks to mend their hurtful ways.

If the behavior of hawks tends to encourage the proliferation of doves, and the behavior of doves tends to encourage the proliferation of hawks, is there some stable mixture of hawks and doves?

Indeed there is. This stable proportion is that at which the average score for hawks is equal to the average score for doves. If we let p equal the proportion of hawks in the population and $1 - p$ equal the proportion of doves, then the average score for hawks is $-225p + 30(1 - p)$ and the average score for doves is $0p + 5(1 - p)$. If we set these 2 scores equal to each other, we find $p = 1/10$. Accordingly, a population of hawks and doves in a ratio of 1:9 is stable, given these utility values. There is no incentive for the immigration of new hawks or doves, or for the behavioral conversion of existing hawks and doves. Actually, these need not be pure mixtures; probabilistic behavior on the part of each individual is all that is needed: 1 hawk and 9 doves is equivalent to 10 "dawks" (aggressive doves that fight like hawks 10% of the time).

Unfortunately, there's a price to be paid for this stability. The average score for a 1:9 mix of hawks and doves is only 4.5 points, compared with 5 points for a pure population of doves. Everyone would do better if they would agree to being doves, but the resultant segregated society would be vulnerable to the treachery of a single defector. The integrated society is stable precisely because it removes the advantage of defection, and it pays a tithe for this stability.

Our common sense rebels against the unconditional Procrustean behavior patterns of hawks and doves. We like to think we tailor our behavior in some rational way to the situation at hand. Owls, for example, might choose to behave like doves in the company of doves, and like hawks in the company of hawks. Hawks could not take advantage of a population composed entirely of owls, because they would all seem like hawks to them. Similarly, doves could not take advantage of owls because they would all seem like doves to them.

Axelrod subjected the "tit for tat" strategy of the owl to an extensive series of computer simulations.⁹ He showed that tit for tat successfully resisted invasion by a variety of other strategies—many of which were substantially more sophisticated—and concluded that it possessed all the characteristics necessary for the evolution of cooperation. First, the strategy is *nice*; it starts out cooperating, and always reciprocates cooperation. Second, the strategy is *provokable*; it swiftly punishes any breach of cooperation. Third, it is *forgiving*; it does not hold a grudge, and reciprocates cooperation again immediately after imposing punishment. Fourth, it is *simple*; its rules for punishment and reward are readily recognized.

A number of real biological and social examples of tit for tat have been identified,⁹ demonstrating that the

jungle is not inhabited solely by winners and losers. Often, potential competitors share a common set of interests, and lie together in harmony.¹⁰ On the other hand, whenever competitors do not share the same interests, envious strategies (directed more to minimizing the survival of another than to maximizing one's own survival) can also evolve.¹¹

So can outright conflicts of interest.¹¹ Suppose, for example, that an editorial referee and a journal editor (you, dear reader, can supply the ornithological metaphors here—I know who feathers *my* nest) are considering whether or not to publish a revolutionary manuscript that has some small probability, p , of being correct, and $1 - p$ of not being correct (the first report of cold fusion, for example). Call a the gain to the editor if she publishes the paper and it is later verified, and call b the loss to the editor if she publishes the paper and it is later refuted. If we define utility as the net gain associated with publication and verification minus the net loss associated with publication and refutation (assuming the losses associated with rejection are negligible), the editor's utility is $ap - b(1 - p)$. As long as this utility is positive, the editor should publish the manuscript, and this occurs whenever $p > b/(a + b)$. Similarly, call c the gain to the referee if he recommends publication and it is later verified, and call d the loss to the referee if he recommends publication and it is later refuted. By the same reasoning, the referee's utility is $cp - d(1 - p)$. As long as this utility is positive the referee should recommend publication, and this occurs whenever $p > d/(c + d)$. When $d/(c + d) > p > b/(a + b)$, however, the preferences of the referee and the editor will be in conflict: the editor has more to gain by publishing, while the referee has more to gain by not recommending publication.

How can we better manage the ecology of this jungle? We can begin by taking a census of the number of hawks and doves and owls, and thereby determine if there really is a problem that needs to be managed.^{5,12} But we would also need to enumerate all the utilities, and this is no easy task. These utilities are highly subjective, probably subconscious, and not likely to be volunteered freely even if they are known. It might be easier to discover a hawk's sexual inclinations than its ethical motivations.

Even if we did conduct a comprehensive census, and obtained a full and accurate audit of the utilities, could we use the information effectively? If we knew the utilities, we could calculate the optimal proportion of hawks and doves required for stability, but the result might be too high for us to stomach. Do we really want to live in a society populated by so many hawks, even if it is a stable society?

We could legislate changes in the utilities that would tend to drive down the proportion of hawks, but the magnitude of such changes would have to be substantial. To reduce the proportion of hawks from 10% to 1%, for example, would require us to increase the cost of losing from -480 points to -4,980 points (changing the reward for winning will not do it). Are we prepared to exact such Draconian penalties?

Even if we *could* change the numbers, *should* we change them? Recall that a society of self-satisfied doves is easy prey for a single clever hawk. What effect would legislated ethical sanctions have on the behavior of the existing flock of doves, and on the likelihood that new doves and owls will choose to enter the jungle?

Until the appropriate environmental impact studies are done, I am inclined to think we should leave the academic jungle pretty much alone, trusting that the wildlife there will evolve optimal cooperative strategies on its own (the recent flurry of transgressions notwithstanding). This is not a libertarian call for anarchy, but an enlightened doctrine of *laissez faire*. The time-honored safeguards—scholarly peer review, the public disclosure of conflicts and the pointed letter to the editor—should, of course, continue. But the underlying structure of our jungle always has been—and must continue to be—founded on trust, not on hastily written restrictive regulations that evince a presumption of guilt.¹³

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Dobutamine and Improvement of Regional and Global Left Ventricular Function in Coronary Artery Disease

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The effects of dobutamine infusion on left ventricular (L-V) function in patients with coronary artery disease (CAD) have not been completely defined. Some studies have suggested that dobutamine infusion can be used to achieve a significant increase in myocardial oxygen demand in the presence of severe stenosis, revealing physiologically significant ischemia.¹⁻³ This would be particularly desirable as an alternative to exercise stress testing because some patients are unable to achieve target heart rates due to insufficient motivation, poor physical condition or peripheral vascular disease. Studies with contrast ventriculography using postextrasystolic stimulation and epinephrine infusion have suggested that viable, but poorly contracting myocardium, often responds to these stimuli and can thus be differentiated from infarcted, irreversibly injured myocardium.^{4,5} The pharmacologic profile of dobutamine as a relatively selective β -1 agonist⁶ suggests that dobutamine also may stimulate viable but "hibernating" myocardium.⁵ In this report, the effects of dobutamine infusion on global LV ejection fraction and abnormal LV regional wall motion have been assessed in 15 patients with coronary artery disease. The goal of the study was to determine whether dobutamine "stress" would induce a diminished LV ejection fraction and provoke new LV wall motion abnormalities or improve global and/or regional LV dysfunction.

The protocol and consent form were approved by the Human Subjects Review Committee. Patients who had angiographically proven CAD and regional LV dysfunction were referred for evaluation. Patients were excluded if they had unstable angina, severe arrhythmias, valvular heart disease or systemic hypertension (defined as systolic arterial pressure of ≥ 180 mm Hg or diastolic arterial pressure of ≥ 100 mm Hg). Cardiovascular drugs were continued. The electrocardiogram and blood pressure were recorded every 2 minutes. Red blood cells were labeled *in vivo* with 25 to 30 mCi of technetium-99m after administration of a stannous agent.⁷ Baseline equilibrium radionuclide angiography was performed at rest in the supine position in the anterior, 45° left anterior oblique with a caudal tilt of 10 to 30° and in the 70° left anterior oblique projections. Data were acquired in the frame mode of 64 × 64 matrix, dividing the cardiac cycle into 32 equal intervals. Extrasystoles were rejected. Initially, the dobutamine dose was at 5 μ g/kg/min

and was then increased to 10 and 20 μ g/kg/min after 5 and 18 minutes of infusion, respectively. Infusion was terminated for angina, significant arrhythmia or severe hypertension (systolic blood pressure ≥ 230 mm Hg or diastolic pressure of 120 mm Hg). The anterior and left anterior oblique 45° equilibrium radionuclide angiograms were obtained 5 minutes after both 10 and 20 μ g/kg/min of dobutamine infusions. Regional wall motion was assessed by examination of dynamic images and global LV ejection fractions were calculated by 2 independent observers and a consensus was reached.

Results are expressed as mean \pm standard error of the mean. Baseline and dobutamine 10 and 20 μ g/kg/min values for hemodynamics and ejection fractions were compared using 2-way analysis of variance followed by Duncan's Multiple Range test. A *p* value < 0.05 was considered statistically significant.

Baseline studies and the effects of dobutamine infusion for the 15 patients are listed in Table I along with summary statistics. Dobutamine significantly decreased the LV ejection fraction in only 1 patient. Overall, dobutamine significantly increased mean LV ejection fraction at infusion rates of both 10 and 20 μ g/kg/min in this patient population. Nine of the 15 patients with 10 μ g/kg/min of dobutamine and 11 with 20 μ g/kg/min of dobutamine infusion had clinically significant increases in the LV ejection fraction of ≥ 0.05 . In addition, 8 of 11 patients with improved LV ejection fraction showed improvement of an asynergic wall region. In 1 patient, deterioration of regional wall motion was observed when the dobutamine infusion rate was increased from 10 to 20 μ g/kg/min. Hemodynamic effects on systolic arterial pressure and heart rate were dose-dependent while the LV ejection fraction failed to increase significantly from when infusion rates were increased from 10 to 20 μ g/kg/min of dobutamine.

No ventricular tachycardia was encountered. In 3 patients, additional ST-segment depression was observed, as listed in Table I. These electrocardiographic changes were observed in 1 patient with no improvement in regional and global LV function. One patient had 0.5 to 1.5 mm additional ST-segment depression during an infusion rate of 20 μ g/kg/min of dobutamine, with an accompanying decrease of LV ejection fraction and deterioration of LV regional wall motion. The third patient with additional ST-segment depression showed improvement of regional and global LV function at dobutamine infusion rates of both 10 and 20 μ g/kg/min.

Three patients who showed improved LV ejection fraction plus improvement in regional wall motion after dobutamine radionuclide angiography were referred for

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TABLE I Effects of Dobutamine Infusion on Hemodynamics and Ejection Fraction in Patients with Coronary Artery Disease

Patient	Age (yr) & Sex	Regional Improvement of Left Ventricle	Baseline				Dobutamine (10 μ g)				Dobutamine (20 μ g)				ECG Changes
			HR	SAP	DAP	LVEF	HR	SAP	DAP	LVEF	HR	SAP	DAP	LVEF	
1	66M	0	62	100	60	0.17	85	140	80	0.18	130	134	70	0.19	+
2	49M	+	75	120	80	0.25	90	130	80	0.35	105	146	80	0.30	+
3	31M	+	74	120	70	0.32	67	190	60	0.45	81	210	80	0.48	—
4	48M	0	86	110	78	0.31	105	146	90	0.38	130	152	90	0.47	—
5	63F	0	89	134	90	0.21	104	162	94	0.25	118	166	90	0.29	—
6	70M	+	74	112	80	0.30	81	166	60	0.48	96	172	70	0.50	—
7	40M	+	57	142	90	0.57	86	194	100	0.81	110	192	88	0.84	—
8	65M	0	92	120	65	0.17	120	132	90	0.18	150	126	72	0.17	—
9	58M	+	81	110	80	0.19	104	110	70	0.23	113	116	80	0.25	—
10	45M	+	93	112	82	0.32	98	120	80	0.38	100	140	90	0.37	+
11	45M	+	84	104	70	0.17	87	110	70	0.22	104	150	80	0.25	—
12	54M	0	74	118	80	0.50	84	140	80	0.58	96	180	80	0.61	—
13	54F	+	83	102	65	0.36	78	106	60	0.42	88	105	57	0.42	—
14	70M	—	57	131	66	0.37	50	178	81	0.34	60	187	87	0.31	—
15	62F	0	75	102	62	0.26	85	92	58	0.26	93	91	42	0.27	—
\bar{x}			77*	116	74	0.30	89†	141†	77	0.37†	105†*	151†	77	0.38†	
SEM			3	3	2	0.03	4	8	3	0.04	6	8	3	0.05	

* Mean \pm standard error of the mean; † significantly different from baseline by 2-way analysis of variance Duncan Multiple Range test; ‡ significantly different from dobutamine (p < 0.05) 10 μ g/kg by 2-way analysis of variance.
ECG = electrocardiographic; HR = heart rate; LVEF = left ventricular ejection fraction; SAP-DAP = systolic-diastolic arterial pressure.

coronary artery revascularization; 1 underwent coronary angioplasty and 2 had coronary artery bypass grafting. Subsequently, 2 to 4 weeks after coronary revascularization, radionuclide angiography showed recovery of regional and global LV function to levels seen during dobutamine infusion. One of these patients had deterioration of LV regional wall motion and global function when dobutamine dose was increased from 10 to 20 μ g/kg/min. In this patient, after revascularization, there was recovery of regional and global LV function to the level seen during the 10 μ g/kg/min of dobutamine infusion.

Our data show that dobutamine infusion of 10 and 20 μ g/kg/min in patients with regional and global LV dysfunction adversely affected LV ejection fraction in only 1 patient. Instead, significant increases of LV ejection fraction were observed in 11 of our 15 patients. Improved regional wall motion in asynergic regions also was observed in many patients. In all 3 cases referred for coronary revascularization, recovery of regional and global LV function to levels achieved during dobutamine radionuclide angiography was observed. Dobutamine radionuclide angiography was not associated with significant adverse responses. Additional ST-segment depressions were observed in 3 patients.

There is some controversy regarding the effect of dobutamine on cardiac function in patients with coronary artery disease. Two echocardiographic studies have used dobutamine infusion in patients with CAD who were unable to exercise.^{1,2} The patient population in both reports was chosen for postinfarction evaluation of residual coronary disease. In both studies, abnormal wall motion and decreased wall thickening were observed during dobutamine infusion. Dobutamine stress testing was considered an alternative to exercise testing in such patients after myocardial infarction. Additionally, Freeman et al³ have described the use of dobutamine infusion compared to supine bicycle exercise testing using radionuclide angiography. They concluded that incremental dobutamine

infusions were nearly equal in accuracy and sensitivity to exercise. An experimental canine study also has suggested that dobutamine infusion was associated with depressed regional function distal to a critical coronary stenosis.⁸ On the basis of these reports, different results would have been expected from our study.

There are reports, however, supporting the present observations. Bendersky et al⁹ showed that dobutamine infusion at 10 μ g/kg/min improved LV function in patients with chronic heart failure due to ischemic heart disease. In their study, changes in contractile state were not evaluated directly. In all of their patients, stroke volume and stroke work indexes increased while pulmonary arterial wedge pressure tended to decrease during dobutamine infusion. In 7 of the 8 patients in the study by Bendersky et al,⁹ improved LV function was associated with increased myocardial oxygen consumption. Despite this increased metabolic cost, overt myocardial ischemia was observed infrequently. Rabinovitch et al¹⁰ have reported that resting ejection fraction was increased in 18 of the 20 CAD patients after dobutamine infusion of 5 μ g/kg/min. Only 2 of the 20 patients in the study of Rabinovitch et al¹⁰ had a decrease in LV ejection fraction and 1 of these 2 patients showed the appearance of a new wall motion abnormality at a dobutamine infusion of 5 μ g/kg/min. Pozen et al¹¹ studied 18 patients with CAD and congestive heart failure during infusion of dobutamine in doses of 2.5 to 15 μ g/kg/min. In this study, improvement in 27% of the abnormally contracting segments was seen during dobutamine infusion. These studies and our results suggest that the inotropic effects of β -1 adrenergic stimulation by dobutamine can improve ventricular performance in patients with CAD.

Inotropic stimuli such as postextrasystolic potentiation and epinephrine infusion can produce improved regional myocardial wall motion in some patients with CAD.⁴ This has been attributed to "hibernating" myocardium,⁵ defined as persistently impaired LV function at

rest that can be restored to normal by improved blood flow or decreased demand. The differentiation of viable but stunned or hibernating myocardium from necrotic myocardium is desirable in deciding whether coronary artery revascularization is appropriate.⁵ At present, abnormal LV wall motion in regions with preserved glucose uptake, determined with positron emission tomography, is considered to be hibernating myocardium that will recover function with revascularization.¹² However, the availability of this test is limited by resources and cost. A potential alternative is delayed tomographic myocardial thallium-201 imaging to differentiate viable and nonviable myocardium.¹³ This test can require delayed imaging beyond 24 hours, which presents technical and practical difficulties. Compared with these studies, the dobutamine test has advantages in that dobutamine is relatively cheap, easily administered, has a short half-life of 2 minutes⁶ and is used commonly by cardiologists. Our study suggests that dobutamine radionuclide angiography may be an attractive alternative to other tests in detecting ischemic but viable myocardium potentially suitable for coronary artery revascularization.

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Semiselective Angiography of the Internal Mammary Arteries as a Preparation for Coronary Bypass Surgery

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Internal mammary artery grafting in coronary artery bypass surgery has resulted in increased long-term patency and improved survival compared to venous bypass grafting. Angiography of the mammary arteries before bypass surgery is considered to be superfluous because they are rarely affected by atherosclerosis.¹ There are, however, no data on how often an internal mammary artery graft is intraoperatively rejected because of insufficient sluggish flow due to atherosclerosis. Early postoperative graft failure is said to be mainly related to technical errors.^{2,3} To establish the frequency of atherosclerotic

changes in the subclavian and internal mammary arteries among our patients, we performed semiselective angiography on both mammary arteries during cardiac catheterization in candidates for bypass surgery.

One hundred five consecutive patients (87 men and 18 women) aged 35 to 80 years (median 58) were studied. Sixty-five patients (62%) had 3-vessel disease, 25 (24%) had 2-vessel disease and 15 (14%) had 1-vessel disease. In all patients semiselective angiography of both mammary arteries, performed with a standard 5Fr right Judkins diagnostic catheter, complemented the coronary artery procedure. Ten ml of undiluted contrast medium was injected manually with the catheter tip as near as possible to the origin of the internal mammary artery. Only posteroanterior views were used, documented on 35-mm cinefilm. Significant atherosclerosis was defined as a diameter reduction of $\geq 50\%$. In 13 patients the imaging quality of the right mammary artery was insuf-

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ficient; thus, 105 left and 92 right vessels were studied. We saw a stenosis in the proximal part of the internal mammary artery in only 1 patient (0.95%), a 43-year-old woman with lipodystrophy. There were no significant subclavian artery stenoses proximal to the internal mammary artery, and only 2 patients (1.9%) had stenoses distal to the origin of the mammary arteries.

Routine postmortem studies^{4,5} show $\geq 50\%$ narrowing of the lumen in 0 to 5% of the cases. Routine preoperative angiography of the internal mammary artery has seldom been done. The only reported study⁶ of patients with coronary artery disease showed a 2% incidence of atherosclerosis in the mammary arteries and a 4% incidence of atherosclerosis in the subclavian arteries. Our results showed an even lower incidence of these pathologic changes. Even in older patients, in whom atherosclerosis

is usually advanced, no pathology of the mammary arteries was found. It seems that routine preoperative angiography of the mammary artery is indeed unnecessary.

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Possible Atrial Proarrhythmic Effects of Class 1C Antiarrhythmic Drugs

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The class 1C antiarrhythmic drugs encainide and flecainide have been used to treat ventricular arrhythmias.^{1,2} Although not currently approved, they are also being used in the treatment of atrial arrhythmias.^{3,4} This antiarrhythmic action results from a marked depressant effect on conduction velocity and a moderate effect on prolonging refractoriness in the myocardium.^{5,6} This marked depression of conduction velocity also results in the highest incidence of ventricular proarrhythmic effects observed with any class of antiarrhythmic drug.^{7,8} However, less is known regarding their potential to produce atrial proarrhythmic effects.^{3,4} Recently we observed 6 patients who were being treated with flecainide or encainide for preexisting ventricular or atrial arrhythmias, and who developed new or modified symptomatic atrial arrhythmias with a rapid ventricular response. In 2 cases, life-threatening consequences arose from the arrhythmia. The clinical details of these cases are presented and the potential mechanisms of the atrial proarrhythmic effects of the 1C drugs are discussed.

Patients with new or modified atrial arrhythmias

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developing during therapy with encainide or flecainide were admitted to the hospital. Digoxin was administered when appropriate to slow the ventricular response. The type 1C antiarrhythmic drug was immediately discontinued. Continuous electrocardiographic monitoring was performed and blood samples were obtained for serum chemistry and hematology, including cardiac enzymes. A chest radiograph was obtained. A 12-lead electrocardiogram was performed on each day of hospitalization. Hemodynamically stable patients were observed for ≥ 24 hours after withdrawal of the 1C drug. If the patients did not revert spontaneously to sinus rhythm, they received an alternative antiarrhythmic drug or direct current cardioversion. Hemodynamically unstable patients underwent immediate direct current conversion. The patients were then discharged home on an alternative antiarrhythmic drug for their baseline arrhythmia (or in 1 case, no therapy) and were followed in the outpatient clinic for symptomatic and/or electrocardiographic evidence of recurrence of the presenting arrhythmia.

New or modified atrial arrhythmias were defined in the following manner: atrial flutter⁹ was defined by a regular saw-toothed pattern of P waves on electrocardiogram, inverted in the inferior leads II, III or aVF at a rate of ≥ 240 beats/min; and atrial tachycardia was defined by a regular P-wave pattern at a rate < 240 beats/min.

To determine the frequency with which these new arrhythmias were occurring, a computer search of pharmacy records identified all patients who had received

TABLE I Clinical Characteristics of Patients

Patient No.	Age (yr) & Sex	Cardiovascular Diagnoses	EF (%)	ECG Findings and Abnormalities	AA Drug and Dose (mg/day)	Duration on 1C Drug (months)
1	71M	SH, AR, AVR	30	1-AVBLK, LBBB	FL (200)	24
2	64F	SH, MVP	65	NSST, PRWP	E (100) M (100)	2
3	67M	MR	76	PRWP, ST(DEP)	FL (300) D (0.2)	2
4	61M	CAD, MI, CABG	30	AMI, IMI, NSST	E (75)	1
5	61M	COPD	58	LOW VOLTAGE QRS	E (75)	1/4
6	77M	CAD, MI	NA*	PRWP, ST(DEP)	E (150) D (0.2)	24

* Angiographic ejection fraction (EF) not available, but 2-dimensional echocardiogram showed mild global decrease in EF and hypokinesis of the septum.

AA = antiarrhythmic; AMI = anterior myocardial infarction; AR = aortic regurgitation; AVR = aortic valve replacement; CAD = coronary artery disease; CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; D = digoxin; E = encainide; ECG = electrocardiogram; EF = ejection fraction; FL = flecainide; IMI = inferior myocardial infarction; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; M = metoprolol; MI = history of myocardial infarction; MR = moderate mitral regurgitation; MVP = mitral valve prolapse; NA = not available; NSST = nonspecific ST and T-wave abnormalities; PRWP = poor R-wave progression; SH = systemic hypertension; ST(DEP) = ST depression; 1-AVBLK = first-degree atrioventricular block.

TABLE II Characteristics of Prior and Current Arrhythmias

Patient No.	Baseline Arrhythmia (Duration, months)	Previous Therapy Failed	Presenting Arrhythmia on 1C Drug	Presenting Symptoms	Heart Rate on 1C Drug (A/V BPMmax)	Treatment of SVT on 1C Drug	Response to Treatment
1	NSVT (24)	P, Q	AT	SOB, LH	170/170	D/C 1c, D	SR
2	PAF (24)	D, V, Q, P	AFL	SOB, LH, PALP	350/175	D/C 1c, D	SR
3	PAF (29)	D, Q, P	AFL	SOB, CP	240/240	D/C 1c, S	AFIB
4	NSVT (2)	F	AFL	SOB, CP, LH	240/240	D/C 1c, D, P	SR
5	IVT (60)	P, N, L	AFL	PALP	300/150	D/C 1c, S	IVT
6	AF/AFL (65)	Q	AT	LH, PALP	190/190	D/C 1c, DC	SR

AFIB = atrial fibrillation; AFL = atrial flutter; A/V BPMmax = atrial/ventricular beats per minute maximum observed; AT = atrial tachycardia; CP = chest pain; D = digoxin; DC = direct current cardioversion; D/C 1C = discontinue 1C drug; F = flecainide; IVT = incessant hemodynamically tolerated ventricular tachycardia; L = intravenous lidocaine; LH = light-headedness or dizziness; N = N-acetylprocainamide; NSVT = nonsustained ventricular tachycardia and frequent premature ventricular contractions; P = procainamide; PAF = paroxysmal atrial fibrillation; PALP = palpitations; Q = quinidine; S = spontaneous conversion of arrhythmia after withdrawal of 1C drug; SOB = shortness of breath; SR = sinus rhythm; SVT = presenting supraventricular arrhythmia; V = verapamil.

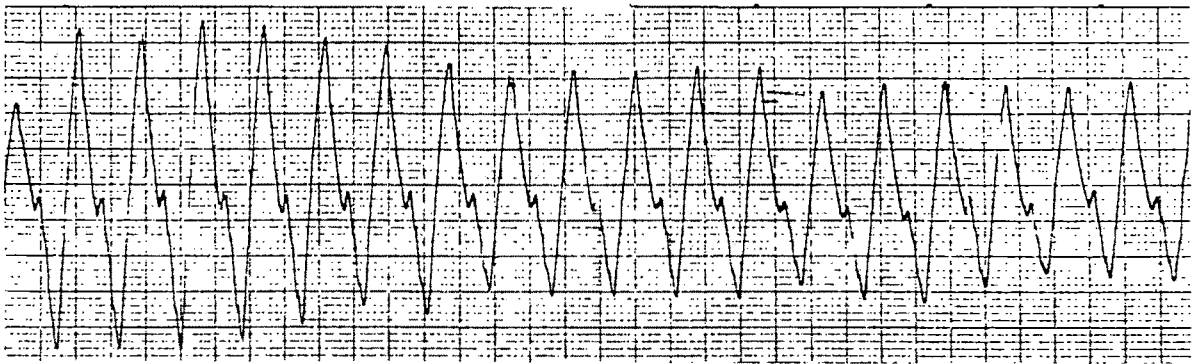
encainide or flecainide at our 2 hospitals (University Medical Center and Veterans Administration Hospital) during the period when these 6 patients presented (from October 1, 1988, to September 30, 1989). Only patients who are initially evaluated and followed at either of these hospitals may receive prescriptions from their respective pharmacies. In addition, the records of all patients receiving encainide or flecainide were reviewed to ensure that frequent follow-up visits had been completed during this time period and the patients were contacted by phone if they had not been seen within 3 months of the end of this time period. The frequency of proarrhythmic effects was then calculated by dividing the number of patients with new arrhythmias by the total number of patients receiving encainide or flecainide.

Six patients (5 men and 1 woman), aged 61 to 77 years (mean 67 ± 5.6), presented with new or modified symptomatic atrial arrhythmias (Tables I and II). Four patients were receiving encainide and 2 were receiving flecainide at the time of presentation. These 6 patients had a history of other refractory arrhythmias that were well documented by multiple clinic visits, 12-lead electrocardiograms and 1 or more 24-hour Holter monitors, over a period ranging from 2 to 65 months before treatment with a 1C drug. Two patients were being treated with a 1C drug for refractory atrial fibrillation, 1 for atrial fibrillation and flutter, 2 for nonsustained ventricular tachycardia and 1 for a slow incessant ventricular

tachycardia (documented by electrophysiology study). The 3 patients being treated for ventricular arrhythmias had not previously had any documented supraventricular arrhythmias. All patients had underlying structural heart disease or coronary artery disease. Left ventricular function was decreased moderately to markedly in 3 patients, but was normal in 3. No patient had congestive heart failure at presentation. Serum chemistries and hematology studies were normal in all patients. Serum levels of the 1C drugs were not obtained.

All 6 patients developed symptoms related to their new or modified atrial arrhythmia (Table II). In 4, they were severe (numbers 1, 2, 4 and 6) and required urgent treatment. These symptoms were notably worse than those caused by their original arrhythmias and included palpitations, shortness of breath, chest pain, fatigue, weakness, light-headedness and diaphoresis. Dire hemodynamic consequences were noted in 1 patient (number 6) who had a systolic blood pressure of only 70 mm Hg and in another patient (number 3) who developed a non-Q-wave myocardial infarction diagnosed by CK-MB release (peak CK 350, MB 6%) and T-wave inversion in the inferior leads on the 12-lead electrocardiogram. The new or modified arrhythmias were atrial flutter in 4 patients and atrial tachycardia in 2 (Table II). The ventricular response was 1:1 in 4 patients (2 with atrial flutter and 2 with atrial tachycardia) and 2:1 in 2 (both with atrial flutter).

A.



B.

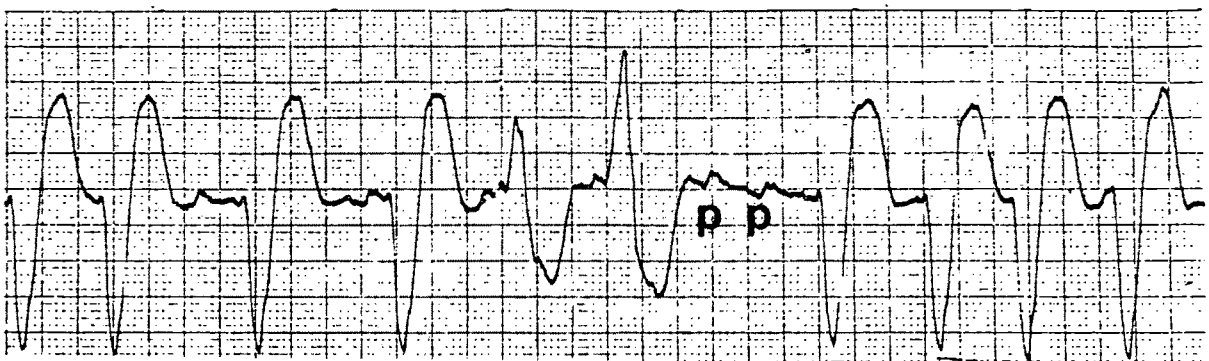
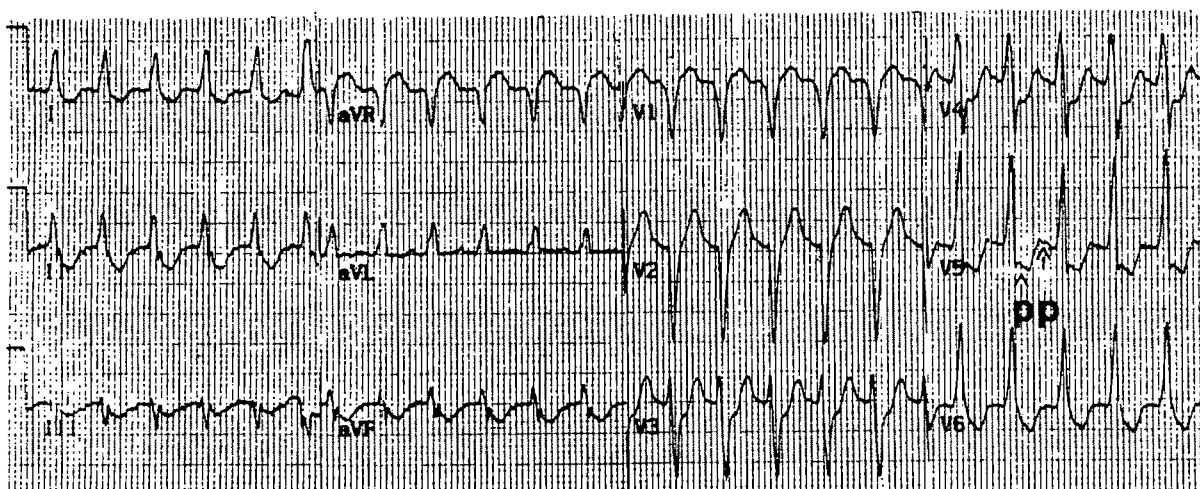


FIGURE 1. A, A rhythm strip is shown from patient number 1, who presented with a rapid, wide-complex tachycardia resembling ventricular tachycardia. However, the QRS morphology was identical to that of the sinus rhythm QRS morphology (underlying left bundle branch block). Heart rate was 170 beats/min. Patient was receiving flecainide for a history of ventricular arrhythmias. B, after intravenous digoxin, ventricular rate slows and becomes irregular. P waves (p) were then discernible at a rate of 170 beats/min, indicating that the initial arrhythmia was an atrial tachycardia with 1:1 atrioventricular conduction, with a prolonged QRS due to left bundle branch block.

An example of a new atrial tachycardia developing in a patient (number 1) with a history of ventricular arrhythmias only is shown in Figure 1. The patient presented with a rapid tachycardia (wide-complex and resembling ventricular tachycardia due to underlying left bundle branch block) at a rate of 170 beats/min. The ventricular response gradually slowed without a change in the QRS morphology after intravenous digoxin, first with appearance of 2:1 atrioventricular conduction and then variable atrioventricular conduction, at which time P waves delineating the underlying atrial tachycardia were clearly visible. Figure 2 shows an example of the development of a regular atrial flutter (atrial rate 350 with a 2:1 ventricular response ratio of 175) in a patient (number 2) who previously had only had paroxysmal atrial fibrillation with a controlled ventricular rate (i.e., <100 beats/min). An example of a new atrial flutter with 1:1 atrioventricular conduction is shown in Figure 3 in a patient (number 4) with a history of only ventricular arrhythmias. The atrial and ventricular rate was 240 beats/min, causing the patient to be markedly symptomatic. Intravenous digoxin slowed the ventricular response to 120 with 2:1 atrioventricular conduction, revealing the underlying flutter waves.

The 1C antiarrhythmic drug was immediately withdrawn in all cases. In the short-term, 3 of the 6 patients (numbers 1, 2 and 4) responded to intravenous digoxin given to relieve symptoms associated with a rapid ventricular response to the atrial tachycardia. One patient (number 6) required urgent direct current cardioversion to sinus rhythm because of hypotension. Two patients did not require short-term treatment, 1 (number 3) due to spontaneous slowing of the ventricular response after admission and 1 (number 5) due to stable hemodynamic status and tolerable symptoms. Two patients (numbers 1 and 2) reverted spontaneously to sinus rhythm, 1 (number 4) required intravenous procainamide infusion, 1 (number 3) reverted to atrial fibrillation and 1 (number 5) reverted to a baseline incessant ventricular tachycardia. Alternative long-term antiarrhythmic therapy was substituted in 5 (including mexiletine in patient number 1, amiodarone in patients number 2 and 5 and procainamide in patients number 4 and 6) and withheld in 1 (patient number 3, who has remained in chronic atrial fibrillation on coumarin and digoxin). During 11 ± 3.2 months of follow-up (range 5 to 15 months), no patient has had a recurrence of the atrial arrhythmia observed while on the 1C drug.

A.



B.

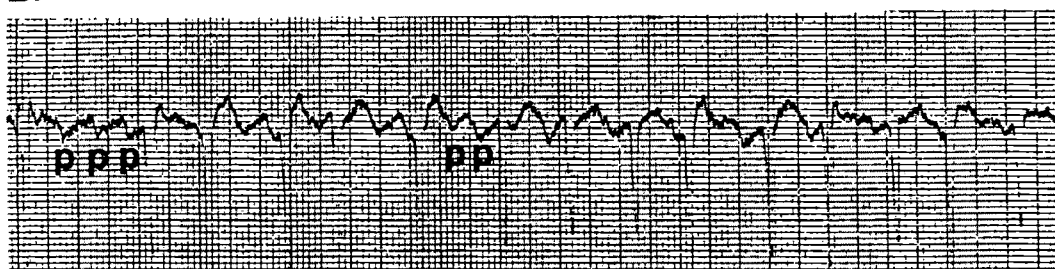


FIGURE 2. A, a 12-lead electrocardiogram is shown from patient number 2, who had a history of only atrial fibrillation with a controlled ventricular response. The patient presented with a rapid regular atrial tachycardia with a ventricular rate of 175. Regular P waves at a rate of 350 are noted (small arrows in lead V₅). B, after intravenous digoxin, ventricular response is slowed and a regular atrial flutter is seen (note P waves). The arrhythmia subsequently converted spontaneously to sinus rhythm (not shown).

A computer search of pharmacy records at both hospitals where these patients were observed from October 1, 1988, to September 30, 1989, revealed that a total of 60 patients received encainide or flecainide for either ventricular or supraventricular arrhythmias. Furthermore, a review of patient charts revealed that all 60 patients were seen and followed in the outpatient clinics at the 2 hospitals during this time. Thus, among those seen and prescribed encainide or flecainide, 6 of 60 (10%) developed symptomatic atrial proarrhythmic effects requiring hospitalization and treatment. The remaining 54 patients had no evidence by review of records and phone contact (which included the history and physical examination, electrocardiograms and Holter monitors in most cases) of any new atrial arrhythmias developing while on encainide or flecainide.

We observed new atrial arrhythmias or modification of preexisting atrial arrhythmias in 6 of 60 patients (10%) receiving the class 1C antiarrhythmic drugs flecainide or encainide. These arrhythmias caused symptoms in all patients and potentially life-threatening complications in some. They occurred in patients being treated for atrial arrhythmias and in patients being treated for ventricular arrhythmias who had not previously had atrial arrhythmias. All of the patients had underlying heart disease, but

they had no other features in common. The new or modified atrial arrhythmias resolved after withdrawal of the 1C drug and have not recurred during long-term follow-up. Digoxin was useful in controlling the rapid ventricular response associated with these arrhythmias.

Previous studies have shown that atrial fibrillation and flutter and some forms of atrial tachycardia are due to reentry.⁹ Furthermore, reentrant arrhythmias usually require a substrate of focally depressed conduction velocity in the myocardium.^{10,11} Therefore, antiarrhythmic drugs such as the 1C drugs that depress conduction velocity may prevent reentrant arrhythmias by producing complete block in the area of slow conduction or they may cause or aggravate reentrant arrhythmias by optimizing slow conduction to facilitate reentry. The ventricular proarrhythmic effects of the 1C drugs have been clearly shown.^{7,8} Several of the patients presented here showed the potential for the 1C drugs to cause new atrial arrhythmias in the absence of a prior history of atrial arrhythmias. This may be an example of facilitation of reentry by depression of atrial conduction velocity.

The slowing of preexisting atrial arrhythmias by the 1C drugs (i.e., the slowing and regularization of atrial fibrillation to atrial flutter and the slowing of atrial flutter to atrial tachycardia as seen in several of these patients) is

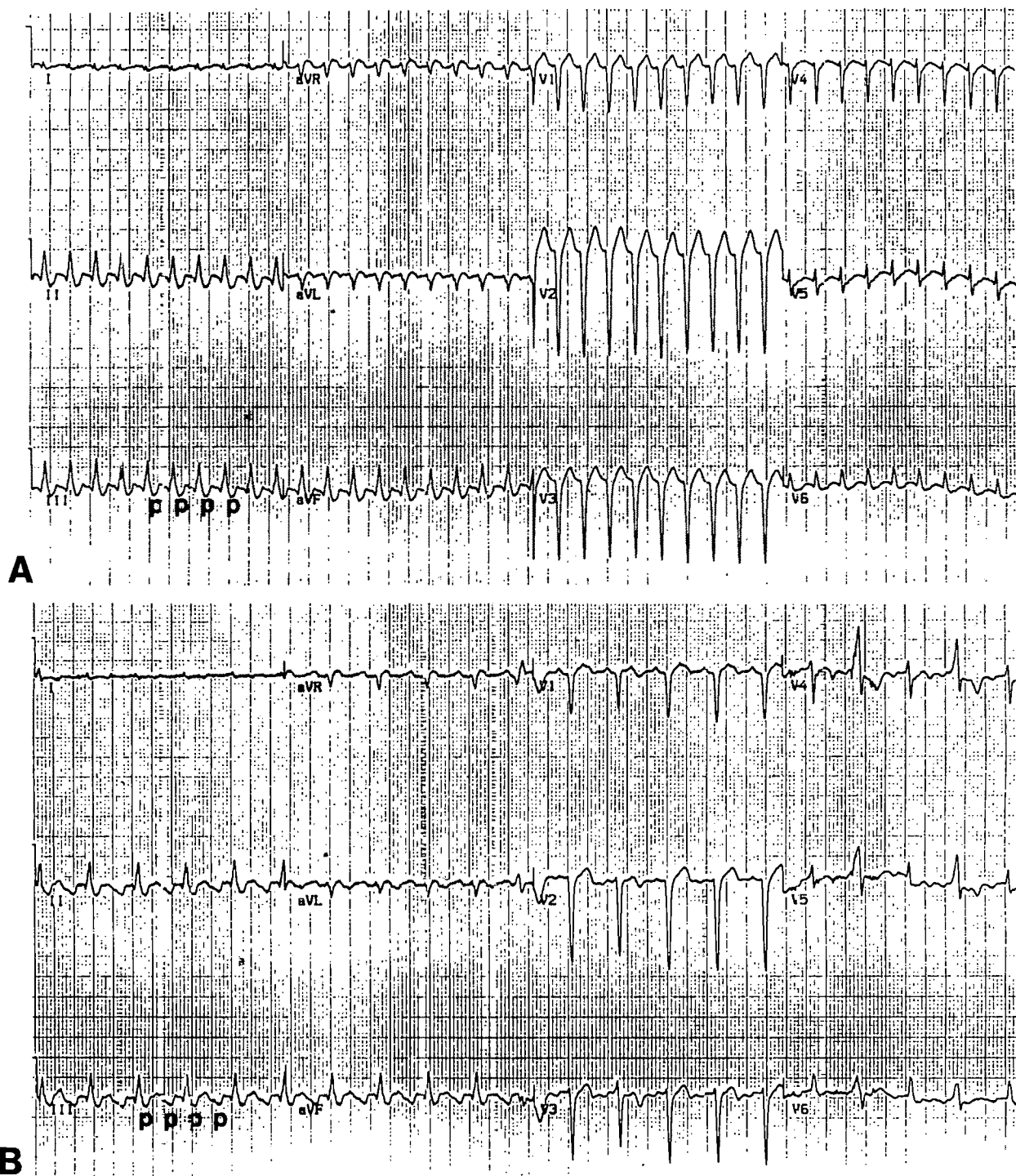


FIGURE 3. *A*, a 12-lead electrocardiogram is shown from patient number 4 who presented with atrial flutter and a 1:1 ventricular response (atrial rate 240 beats/min). This patient was receiving encainide for a history of only ventricular arrhythmias. *B*, a 12-lead electrocardiogram in this same patient is shown after digoxin slowed the ventricular response to 2:1. Typical atrial flutter waves (p) were then clearly seen.

also most likely due to the depression of atrial conduction velocity. Previous studies in a canine model of atrial flutter support this hypothesis.¹² In these studies, slowing of atrial flutter rate correlated with drug-induced depression of conduction velocity.¹² In several of the patients presented here, the slowing of the atrial arrhythmia also resulted in 2:1 or 1:1 atrioventricular conduction with extremely rapid ventricular responses. When this oc-

curred in conjunction with QRS widening, the resultant arrhythmia resembled ventricular tachycardia, a phenomenon which has been previously described.¹³ In contrast to ventricular tachycardia, where slowing of the rate is hemodynamically beneficial, the slowing of atrial arrhythmias can have dire hemodynamic consequences due to acceleration of the ventricular response. The lack of significant effects of the IC drugs on the atrioventricular

node probably accounts for the acceleration of ventricular rate in response to slowing of the atrial rate.

This study was not prospectively designed to assess atrial proarrhythmic effects of the 1C drugs, but rather an analysis of consecutive cases with long-term follow-up after discontinuation of the 1C drug. Therefore, some concern exists regarding the accuracy of the denominator in this study. However, these data were derived from a thorough review of hospital pharmacy records and, although a relatively high percentage (10%) of the patients had atrial proarrhythmic effects, this percentage is similar to that observed in previous studies for ventricular proarrhythmic effects.^{1,2,7,8} These patients also had significant underlying heart disease, which could have predisposed them to potential atrial proarrhythmic effects from the 1C drugs. Whether or not similar effects would be observed in patients without significant underlying structural heart disease is unknown. These cases show the potential for serious or life-threatening atrial proarrhythmic effects when the 1C drugs are used to treat atrial or ventricular arrhythmias. Furthermore, the concomitant use of digoxin or other atrioventricular node blockers to prevent a rapid ventricular response in the event of proarrhythmia may warrant further investigation.

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Journal: Harvey W, Heberden W, Withering W, Stokes W, Murrell W, Einthoven W, Osler W. Anomalies and curiosities of cardiology and of cardiologists. Reflections of famous medical Williams. *Am J Cardiol* 1984;53:900-915.

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READERS' COMMENTS

Fish Oil Supplements and Restenosis After Percutaneous Transluminal Coronary Angioplasty

The study by Milner et al¹ reported a lower incidence of clinical restenosis in patients treated with fish oil supplements after percutaneous transluminal angioplasty (PTCA). These findings differ from those of 2 placebo-controlled trials, by our group² and by Grigg et al,³ which revealed no benefit of fish oil. We believe that the methodology of Milner et al limits the applicability of their findings.

First, the study was unblinded, and used subjective endpoints (symptoms and exercise testing). There was no difference in the single objective endpoint, angiographic restenosis, between the 2 groups (18 vs 26% and 20 vs 26% by intention to treat). Other endpoints (such as the exercise test) were apparently interpreted with knowledge of the randomization status, and by a mix of both the investigators and by other physicians as well. Second, patients were chosen for the study after PTCA, leading to potential selection bias in not approaching patients with less-than-favorable (although successful) PTCA results. Third, study medication was started 1 day after PTCA and no biologic assessment of compliance was undertaken. Membrane levels of n-3 fatty acids adequate to inhibit platelet function and alter eicosanoid formation are achieved only several days to several weeks after initiation of fish oil therapy,^{4,5} whereas platelet aggregation and release of growth factors is greatest in the first 4 days after experimental balloon injury.⁶ For this reason, a large National Institutes of Health-supported trial of fish oil in patients undergoing PTCA will apparently have patients initiate study medication 2 weeks before scheduled PTCA.

For these reasons, and because several studies, including our own, have demonstrated increases in low-density lipoprotein cholesterol levels with fish oil supplementation, we continue to urge that fish oil not be administered to patients undergoing PTCA, pending results of further studies.

Gregg J. Reis, MD
Richard C. Pasternak, MD
Boston, Massachusetts
14 August 1989

1. Milner MR, Gallino RA, Leffingwell A, Pichard AD, Brooks-Robinson S, Rosenberg J, Little T, Lindsay J. Usefulness of fish oil supplements in preventing clinical evidence of restenosis after percutaneous transluminal angioplasty. *Am J Cardiol* 1989;54:294-299.

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2. Reis GJ, Sipperly ME, Boucher TM, Silverman DI, McCabe CH, Baim DS, Sacks FM, Grossman W, Pasternak RC. Randomised trial of fish oil for prevention of restenosis after coronary angioplasty. *Lancet* 1989;2:177-181.

3. Grigg LE, Kay TWH, Valentine PA, Larkins R, Flower DJ, Manolas EG, O'Dea K, Sinclair AJ, Hopper JL, Hunt D. Determinants of restenosis and lack of effect of dietary supplementation with eicosapentaenoic acid on incidence of coronary artery restenosis after angioplasty. *JACC* 1988;12:1073-1078.

4. Von Schacky C, Fisher S, Weber PC. Long-term effects of dietary omega-3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in man. *J Clin Invest* 1985;76:1626-1631.

5. Von Schacky C, Weber PC. Metabolism and effects on platelet function of the purified eicosapentaenoic and docosahexaenoic acids in humans. *J Clin Invest* 1985;76:2446-2450.

6. Steele PM, Chesbro JH, Stanson AW, Holmes DR, Dewanjee MK, Bademon L, Fuster V. Balloon angioplasty: natural history of the pathophysiological response to injury in a pig model. *Circ Res* 1985;57:105-112.

REPLY: We agree that further studies are needed to assess the role of omega 3 fatty acids ("fish oil") in preventing restenosis after successful percutaneous transluminal coronary angioplasty (PTCA). As our article states, and as Reis and Pasternak note, 2 randomized trials demonstrated no benefit from omega 3 fatty acid supplements when compared to "placebo."^{1,2} There are, in addition to our study, 2 that suggest a benefit from fish oil supplements.^{3,4} Of these 5 trials, only 2 used cardiac catheterization as the endpoint for assessing success or failure.^{2,3} The results for these 2 trials were discordant.

It is possible that the lack of placebo may have introduced ascertainment bias in our trial and 2 others.^{3,4} In fact, neither placebo-controlled study^{1,2} demonstrated a benefit from fish oil supplements. There is, however, a question as to what an appropriate placebo might be. Both placebo studies used olive oil (alone, or with corn oil), a product high in monounsaturated fats, substances that in themselves may have antiatherogenic effects.⁵ Reis et al¹ reported a catheterization restenosis rate in the placebo group of 23%, a rate rather better than is usual after PTCA.⁶ In addition, true blinding may be impossible because of the distinct breath, odor and taste accompanying fish oil ingestion.

Our study was limited to subjects with typical angina before PTCA. This design was chosen to provide a clear clinical marker for restenosis, namely return of angina. As cited in our article, silent recurrence is to be anticipated but should occur with equal frequency in treated and control patients in a randomized trial. With regard to the potential for selection bias, randomization to fish oil or control was carried out after entry into the study so that patients with favorable clinical or angiographic features were evenly distributed.

As Reis and Pasternak state, fish oil therapy was not initiated before PTCA. We do not believe fish oil primarily affects

platelets or spasm, the bases for early (48 hours) reclosure. (Note: Agents such as calcium antagonists and aspirin, which are more potent for spasm prevention or platelet inhibition, do not lower the 6-month restenosis rate.) Rather, we suspect that its major effect on preventing restenosis is due to the inhibition of smooth muscle proliferation.^{7,8} Since restenosis occurs usually 1 to 6 months after PTCA, perhaps omega 3 supplements decelerate the growth of the coronary plaque during this time period. Moreover, the peak effect of fish oil supplements usually does not occur for 3 to 6 weeks. Therefore, beginning fish oil supplements 1 to 7 days before PTCA may have no major advantage over initiating therapy the day of PTCA. It would seem ideal to have a clinical trial that initiated fish oil supplements 3 to 4 weeks before PTCA (as has been done in animal experiments⁹).

Finally, it is clear that low-density lipoprotein cholesterol may increase with administration of fish oil supplements.¹⁰ This finding is usually noted when fish oil is given as supplements alone, and not when there is, in addition, a decrease in dietary fats. It is interesting that populations with a high fish intake have a lower incidence of coronary disease for any given level of serum cholesterol, suggesting that the risk of a specific cholesterol level may depend on the dietary sources of fatty acids.¹¹

In summary, <400 subjects have received fish oil supplements during randomized trials¹⁻⁵ to assess coronary restenosis. No other medical therapy tested to date has demonstrated any significant effect on preventing PTCA restenosis. We join Reis and his associates in eagerly awaiting the results of other trials assessing the potential role of omega 3 fatty acids.

Mark Robert Milner, MD
Joseph Lindsay, Jr., MD
Washington, DC
28 August 1989

1. Reis GJ, Sipperly ME, Boucher TM, McCabe CH, Sacks AM, Silverman DI, Baim DS, Grossman W, Pasternak RC. Randomised trial of fish oil for prevention of restenosis after coronary angioplasty. *Lancet* 1989;2:177-181.

2. Grigg LE, Kay TWH, Valentine PA. Determinants of restenosis and lack of effect of dietary supplementation with eicosapentaenoic acid on the incidence of coronary artery restenosis after angioplasty. *JACC* 1989;13:665-672.

3. Dehmer GJ, Popma JJ, Van den Berg EK, Eichhorn EJ, Prewitt JB, Campbell WB, Jennings L, Willerson JT, Schmitz JM. Reduction in the rate of early restenosis after coronary angioplasty by a diet supplemented with n-3 fatty acids. *N Engl J Med* 1988;319:733-740.

4. Slack JD, Pinkerton CA, Van Tassel J, Orr CM, Scott M, Allen B, Nasser WK. Can oral fish oil supplement minimize restenosis after percutaneous transluminal coronary angioplasty? (abstr). *JACC* 1987;9:64A.

5. Leth-Espensen P, Stender S, Ravn H, Kjeldsen K. Antiatherogenic effect of olive and corn oils in cholesterol-fed rabbits with the same plasma cholesterol levels. *Arteriosclerosis* 1988;8:281-287.

READERS' COMMENTS

6. Blackshear JL, O'Callaghan WG, Califf RM. Medical approaches to prevention of restenosis after coronary angioplasty. *JACC* 1987;9:834-848.
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10. Harris WS, Dujoine CA, Zucker M, Johnson B. Effects of a low saturated fat, low cholesterol fish oil supplement in hypertriglyceridemic patients. *Ann Intern Med* 1988;109:465-470.
11. Kromhout D, Besschieter EB, Coulander CL. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med* 1985;312:1205-1209.

Late Morphologic Findings After Coronary Endarterectomy

We read the case report, "Morphologic Changes in Coronary Artery Seen Late After Endarterectomy."¹ The authors point out a number of interesting morphologic changes that occur at coronary artery endarterectomy sites. They suggest that this is the first report of these changes. We would like to bring to the authors' attention an article published in 1988, detailing our experience at the University of Ottawa Heart Institute with the long-term local effects of coronary endarterectomy.² In this report 9 patients of varying age, who survived coronary endarterectomy from 5 to 9 years, were described. These patients, who had varying success with bypass grafting and endarterectomy, provided a unique opportunity to assess the variable long-term effects of this form of arterial injury. Since the accrual of the cases reported in that article, we have reviewed the pathology of another group of approximately 20 patients who have showed similar changes long-term after surgery. These changes vary depending on the anatomic of blood flow after the procedure, but range from early postsurgery thrombosis to long-term patency with superimposed atherosclerosis and its complications.

V.M. Walley, MD
R.W. Byard, MD
W.J. Keon, MD
Ottawa, Ontario, Canada
1: September 1989

1. Kragel AH, McIntosh CM, Roberts WC. Morphologic changes in coronary artery seen late after endarterectomy. *Am J Cardiol* 1989;63:757-759.

2. Byard RW, Keon WJ, Walley VM. Coronary endarterectomy: the long-term local effects. *Am J Cardiovasc Pathol* 1988;2:31-38.

REPLY: We thank Walley, Byard and Keon for pointing out our error. We regret that we overlooked the article "Coronary Endarterectomy: The Long-Term Local Effects." It is, in fact, the first report to detail the changes seen late in coronary arteries after endarterectomy. Their study of 9 necropsy cases elegantly describes and illustrates the changes seen in endarterectomized arteries both proximal and distal to the anastomotic site of saphenous vein bypass grafts. They describe myointimal proliferation typical atherosclerotic plaque and organized thrombus at the site of endarterectomy. Myointimal proliferation (as opposed to typical atherosclerotic plaques), similar to that which we described, were believed to be the most common cause of restenosis.

Amy H. Kragel, MD
William C. Roberts, MD
Bethesda, Maryland
27 September 1989

Plasma Norepinephrine and Treatment of Heart Failure

Kao et al,¹ having investigated the effects of treatment of congestive heart failure (CHF) on the plasma norepinephrine (NE) concentration, concluded that clinical improvement was associated with a reduction in plasma NE levels, while deterioration was associated with an increase. The authors note our results² concerning the importance of several regional contributions to the total abnormality of plasma NE in CHF; they do not consider the finding reported in the same article, which is much more relevant to their study: the plasma NE concentration in CHF is high because of both increased "spillover" or diffusion of NE to plasma (reflecting overall sympathetic nervous system activity³) and reduced plasma clearance of NE. We hypothesized then that the prognostic significance of the plasma NE concentration⁴ depends on progressive impairment of regional blood flow, with consequent reduction of the plasma clearance of NE, as heart failure becomes more severe. We have reviewed the data from our studies of NE kinetics in CHF^{2,5} and now offer evidence in support of the hypothesis, which is equally relevant to the study of Kao et al.

We studied 18 patients with CHF (New York Heart Association class II to IV, left ventricular ejection fraction 9 to 39%, mean 23 ± 10). All studies were done after CHF treatment had been stopped for at least 5 days. The arterial plasma NE concentration was 499 ± 56 (mean \pm standard error) pg/ml. Total NE spillover to plasma was 563 ± 72 ng/min, and plasma clearance of NE was 1.17 ± 0.07 liters/min. These values, as noted in the original publications, differ significantly from those of control subjects; the concentration and spillover rate are high, and the

clearance is low. Figure 1 shows the relations between these parameters and the left ventricular ejection fraction. There is no significant relation between left ventricular ejection fraction and NE spillover to plasma; the relation between the plasma NE concentration and left ventricular ejection fraction therefore depends on that between plasma NE clearance and left ventricular ejection fraction. This is borne out by multilinear regression, in

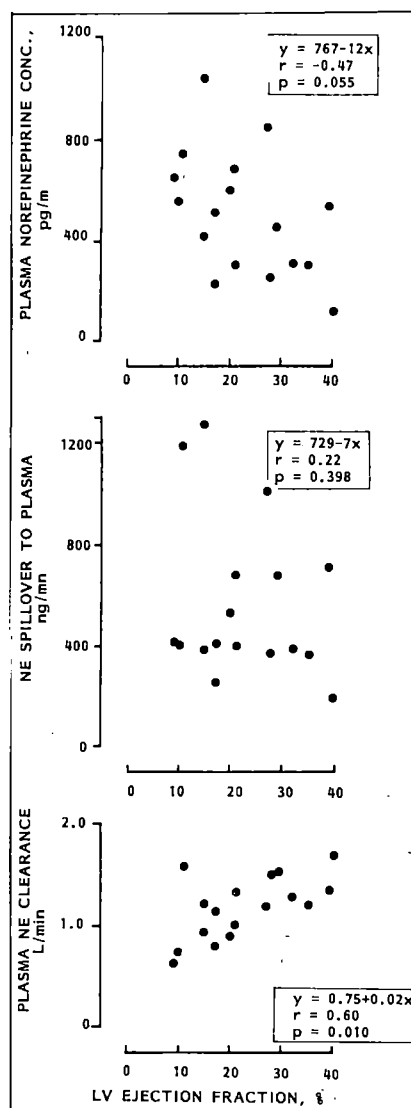


FIGURE 1. Relation between plasma norepinephrine (NE), NE spillover to plasma and plasma NE clearance and left ventricular (LV) ejection fraction.

which only plasma NE clearance retains an independent association with left ventricular ejection fraction.

The response of plasma NE concentration to treatment of CHF is also likely to reflect hemodynamic improvement, or lack thereof, and its effect on regional blood flow and consequently the plasma clearance of NE. There is at present no evidence concerning the effects of drugs

(other than digitalis⁶) on sympathetic function in patients with CHF, which dissociates effects on plasma NE clearance from any putative direct effect on sympathetic nerve activity or NE release.

Gregory J. Hasking, MB, PhD
Newcastle, Australia
Murray D. Esler, MB, PhD
Melbourne, Australia
27 December 1989

1. Kao W, Gheorghide M, Hall V, Goldstein S. Relationship between plasma norepinephrine and response to medical therapy in men with congestive heart failure secondary to coronary artery disease or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1989;64:609-613.
2. Hasking GJ, Esler MD, Jennings GL, Burton D, Johns JA, Korner PI. Norepinephrine spillover to plasma in congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. *Circulation* 1986;73:615-621.
3. Esler M, Jackman G, Bobik A, Kelleher D, Jennings G, Leonard P, Skews H, Korner P. Determination of norepinephrine apparent spillover rate and clearance in humans. *Life Sci* 1979;25:1461-1470.
4. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;311:819-823.
5. Hasking GJ, Esler MD, Jennings GL, Dewar E, Lambert G. Norepinephrine spillover to plasma during steady-state supine bicycle exercise; comparison of patients with congestive heart failure and normal subjects. *Circulation* 1988;78:516-521.
6. Ferguson DW, Berg WJ, Sanders JS, Roach PJ, Kempf JS, Kienle MG. Sympatho-inhibitory responses to digitalis glycosides in heart failure patients: direct evidence from sympathetic neural recordings. *Circulation* 1989;80:65-77.

Usefulness of Echocardiography in Managing Left Ventricular Thrombi After Acute Myocardial Infarction

I found the article by Weintraub and Ba'albaki¹ disappointing for a number of reasons. The decision tree is quite simplistic—currently available microcomputer software programs for decision analysis make model construction and analysis easy. The lower decision tree in Figure 1B gives the impression that one can choose whether to administer anticoagulants despite the presence (or absence) of mural thrombus. When decision models are constructed to examine the clinical value of a diagnostic procedure, one is usually "forced" into action based on the test results: a "positive" result implies treatment, a "negative" result no treatment. To offer a decision node after the results of the echocardiogram is known is thus inconsistent with most techniques of modeling. This type of decision tree should contain only the following 3 choices: (1) anticoagulate all patients; (2) perform echocardiography on all patients; and (3) no anticoagulation and no echocardiography for all patients. The choice for utility scale (patients treated to prevent cerebrovascular accident or extra bleeding) is

cumbersome to translate into a decision tool for the individual patient. The decision tree should contain explicit branches that model the risks of cerebrovascular accident and bleeding as separate chance events that might occur at different times. The choices used for the Results section (All Patients, Positive Echo, Negative Echo, Echo Guided) provide little clinical insight: the Positive Echo choice is always the "best" strategy (minimizes the number of patients treated to prevent a cerebrovascular accident). If one just focuses on the All Patients and Echo Guided choices, the sensitivity analyses show that the All Patients choice is always best—despite the risks of bleeding with or without warfarin. Therefore, the value of the echocardiogram as a management tool is not supported by the results data. The data labeling in Figure 5 is wrong (the All Patients choice should be below the Echo Guided choice, as shown in all other figures), and the X axis of Figure 7 is mislabeled (should be on warfarin, not off warfarin). Finally, the authors omitted a much more extensive model of this whole problem area published in 1983.² The conclusion of this earlier model was that echocardiography was mainly useful in helping to manage patients at risk for mural thrombus who were also at increased risks for bleeding from anticoagulation therapy.

Dennis A. Plante, MD

Burlington, Vermont
6 October 1989

1. Weintraub WS and Ba'albaki HA. Decision analysis concerning the application of echocardiography to the diagnosis and treatment of mural thrombi after anterior myocardial infarction. *Am J Cardiol* 1989;64:708-716.
2. Plante DA, Lau J, Pauker SG. Microcomputer-based medical decision making: echocardiography for ventricular thrombus. *Sem Ultrasound* 1983;4:308.

I applaud Weintraub and Ba'albaki's¹ attempt to clarify the issue of the use of echocardiography in defining the risk of stroke after acute myocardial infarction and to offer rational guidelines for anticoagulant therapy. They allude to the issue of timing of echocardiography. This issue is more acute than suggested. Formation of echocardiographically detected mural thrombus can occur at any time during the first 12 days after an infarction.²⁻⁴ To identify all patients with thrombi, one would either be obliged to perform serial, even daily, echocardiograms in all patients with anterior infarcts (expensive and impractical) or wait until the seventh, tenth or twelfth postinfarct day. Most strokes, however, occur within the first week after an infarct.^{5,6} Thus, any strategy in which anticoagulant therapy is initiated only upon the echocardiographic demonstration of a mural thrombus is unlikely to be practical or effective. A more effective strategy would include early anticoagulation of all anterior Q-wave infarctions and the use of echocardiography to identify candidates for continued anticoagulant therapy. The presence of akine-

sis, dyskinesia or mural thrombus would indicate long-term therapy.

Paul T. Vaitkus, MD
Philadelphia, Pennsylvania

16 October 1989

1. Weintraub WS, Ba'albaki H. Decision analysis concerning the application of echocardiography to the diagnosis and treatment of mural thrombi after anterior wall acute myocardial infarction. *Am J Cardiol* 1989;64:708-716.
2. Asinger RW, Mikell FL, Elsparger J, Hodges M. Incidence of left ventricular thrombosis after acute transmural myocardial infarction. *N Engl J Med* 1981;305:297-302.
3. Arvan S, Bosch K. Prophylactic anticoagulation for left ventricular thrombi after acute myocardial infarction: a prospective randomized trial. *Am Heart J* 1987;113:688-693.
4. Davis MJE, Ireland MA. Effect of early anticoagulation on the frequency of left ventricular thrombi after anterior wall myocardial infarction. *Am J Cardiol* 1986;57:1244-1247.
5. Weinreich DJ, Burk JF, Pauletto FJ. Left ventricular mural thrombi complicating acute myocardial infarction. *Ann Intern Med* 1984;100:789-794.
6. Fulton RM, Duckett K. Plasma-fibrinogen and thromboemboli after myocardial infarction. *Lancet* 1976;2:1161-1164.

REPLY: I found Dr. Plante's comments unfortunate in content and tone. The decision tree is simple, but to call it "simplistic" is not necessary. We disagree that the result of the echocardiogram "forces" any one therapy. It is appropriate that outcome after both positive and negative echocardiogram be considered. In particular, the negative echo model shows the limited use of anticoagulation in these patients. This further strengthens the argument for the "echo guided model." In general, it is appropriate to consider therapy in light of any finding. We further reject Dr. Plante's view of consistency with "most techniques of modeling." There is no one path of scientific inquiry. In developing the model the way we have, we added something slightly different.

We have been most circumspect in balancing cerebrovascular accidents against bleeding. We do not agree that it is inappropriate as a utility scale. What is the major risk of anticoagulation, the major benefit? If the risk of bleeding is not relevant, then Dr. Plante would be right, and all patients should be anticoagulated. This point of view is not consistent with our clinical experience. We do balance bleeding against anticoagulation clinically, generally in the absence of models and published data. Our article is but an attempt to develop how clinicians think about this in a more formal context. We acknowledge that there are imperfections and limitations of the study and the model, but we have been circumspect in our conclusions, allowing the clinician wide latitude in balancing cerebrovascular accidents against bleeding. For Dr. Plante to state that one cannot be compared to the other because they are separate chance events occurring at different times flies in the face of good medical judgement and is potentially harmful to patients.

READERS' COMMENTS

Regarding the article we "missed." *Seminars in Ultrasound* is not a peer reviewed publication and is not listed in the *Index Medicus* or any computerized index. It is unlikely that we would come across it.

I thank Dr. Vaitkus for his supportive comments. I agree that the appropriate strategy is to anticoagulate patients with anterior Q-wave myocardial infarction on admission to the hospital in the absence of contraindications. Echocardiography is most appropriate in guiding the use of long-term oral anticoagulation. I made precisely this point repeatedly throughout the article. I thank Dr. Vaitkus for restating it.

William S. Weintraub, MD
Atlanta, Georgia
17 November 1989

CORRECTIONS

In the June 5, 1989, AJC symposium issue, the address for reprints for Dr. Kinhal's study is incorrect. The correct address is: Vithal Kinhal, MD, 18263 Ten Mile Road, Suite E, Roseville, Michigan 48066. Also, on pages 651 to 671 all LVEFs should read LVET.

The article, "Postmarketing Surveillance in 70,398 Patients Treated with a Triamterene/Hydrochlorothiazide Combination (Maxid)" by Hollenberg and Mickiewicz in the January 17, 1989 symposium issue, on page 40B, has errors in placement of columns in Table V. The three columns under "Response to One-Half Tablet Daily" should be switched with the three columns under "Response to One Tablet Daily". The corrected table is printed below.

The article, "Efficacy and Safety of Triamterene/Hydrochlorothiazide Combinations in Mild Systemic Hypertension" by Schnaper and Maxwell in the January 17, 1989 symposium issue, on page 34B, has an error in Table V. In the first column, under Period 3, triamterene (TMT) should read 75 mg, not 37.5 mg and hydrochlorothiazide (HCTZ) should read 50 mg, not 25 mg. The corrected table is printed below.

TABLE V Results of Nonresponders to TMT (37.5 mg) and HCTZ (25 mg) in Whom Therapy was Changed to TMT (75 mg) and HCTZ (50 mg)

	Mean Sitting Blood Pressure (mm Hg)(±SD)		Mean Sitting Pulse (±SD)
	Systolic	Diastolic	
Period 1 (placebo) (n = 16)	149 (10)	96 (4)	76 (8)
Period 2 TMT 37.5 mg/ HCTZ 25 mg (n = 16)	134 (5)	88 (3)	76 (5)
Period 3 TMT 75 mg/ HCTZ 50 mg (n = 16)	128 (5)	82 (3)	77 (5)
Change Period 3 vs Period 2	-5.4	-5.8	+1.4
p value of change	p < 0.0001	p < 0.0001	NS
Abbreviations as in Table II.			

TABLE V Blood Pressure (BP) Response to a TMT/HCTZ Combination

Grouping of Patients*	n	Response to One-Half Tablet Daily		n	Response to One Tablet Daily	
		Achieved Goal BP (%)	Mean BP Change† (mm Hg)		Achieved Goal BP (%)	Mean BP Change† (mm Hg)
By baseline diastolic BP (mm Hg)						
90-104	2,746	77	-19/-13	9,212	58	-19/-11
105-114	302	55	-29/-22	1,801	49	-29/-20
≥115	48	52	-43/-34	385	36	-39/-28
By age (yr)						
<60 years	1,665	58	-15/-10	6,930	48	-17/-12
≥60 years	1,366	66	-19/-10	4,244	54	-19/-10

* Only patients receiving a fixed dose and who were treated for at least 21 days are included in this analysis.

† Statistically significant change from baseline (p < 0.01, t test).

Abbreviations as in Table I.

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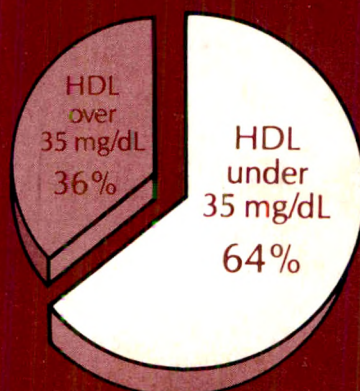
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<35 HDL
mg/dL

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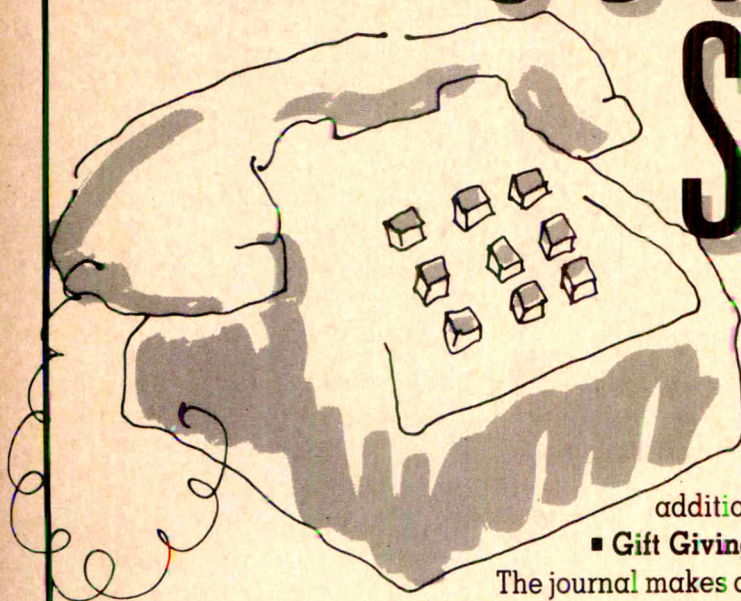
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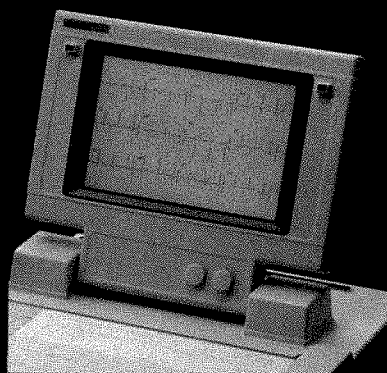
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CORONARY ARTERY DISEASE

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ST Monitoring for Myocardial Ischemia During and After Coronary Angioplasty

Masahiro Mizutani, S. Ben Freedman, Elizabeth Barns, Sadamasa Ogasawara, Brian P. Bailey, and Louis Bernstein

We performed 12-lead electrocardiographic monitoring in 97 patients during percutaneous transluminal coronary angioplasty of a single vessel to correlate ischemic ST changes with clinical, angiographic and coronary hemodynamic variables and to determine the optimum lead or combination of leads for their detection. Our data indicate that ST changes during PTCA may be reliably detected by optimal selection of 3 leads. Occurrence of ischemia is related principally to the vessel dilated and lesion hemodynamics; recurrent ischemia is uncommon immediately after PTCA and may be detected by single-lead ST monitoring.

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Value of Thallium-201 Reinjection After Delayed SPECT Imaging for Predicting Reversible Ischemia After Coronary Artery Bypass Grafting

Hiroshi Ohtani, Nagara Tamaki, Yoshiharu Yonekura, Ishtiaque H. Mohiuddin, Kazuo Hirata, Toshihiko Ban, and Junji Konishi

We evaluated the predictive value of preoperative reinjection thallium-201 imaging for improvement in regional function after coronary artery bypass grafting. After routine stress and 3-hour delayed imaging, 40 MBq of thallium-201 was injected to perform the reinjection tomography in 24 patients before the operation. Our data indicate that the reinjection of thallium-201 should be performed to identify reversible ischemic segments after CABG when routine stress and delayed imaging show no redistribution.

400

Preservation of Left Ventricular Performance with Reduced Ischemic Dysfunction by Intravenous Nisoldipine

Brian P. Kimball, K. Randal Watson, Sanh Bui, and David Frankel

We examined the effect of intravenous nisoldipine on cardiac performance during pacing-induced ischemia in 14 patients with coronary artery disease. The relative contributions of afterload reduction or prevention of myocardial ischemia were assessed using load-dependent global (peak-systolic pressure/end-systolic volume) and regional (peak-systolic pressure/end-systolic radial length) "contractile" indexes. Intravenous nisoldipine maintains ventricular performance during rapid atrial pacing via a combination of systemic vasodilation and amelioration of ischemic myocardial dysfunction.

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Usefulness of Semiquantitative Analysis of Dipyridamole-Thallium-201 Redistribution for Improving Risk Stratification Before Vascular Surgery

John R. Levinson, Charles A. Boucher, Christopher M. Coley, Timothy E. Guiney, H. William Strauss, and Kim A. Eagle

Dipyridamole-thallium-201 scanning is sensitive in identifying patients prone to ischemic cardiac complications after vascular surgery, but its specificity is limited. To determine which patients with redistribution are at highest risk, thallium images were interpreted semiquantitatively in 62 consecutive patients. Our data indicate that determining the extent of redistribution by dipyridamole-thallium-201 scanning improves risk stratification before vascular surgery.

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Management of Complications Associated with a First-Generation Endocardial Defibrillation Lead System for Implantable Cardioverter-Defibrillators

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Characteristic Variation in Evoked Potential Amplitude with Changes in Pacing Stimulus Strength

Anne B. Curtis, Fred Vance, and Kim Miller-Shifrin

Using a computer-based pacing system emulator, we delivered stimuli at various amplitudes to 12 patients through permanent bipolar pacing leads with measurement of the amplitude of the resultant evoked potentials. There is a marked change in the magnitude of the evoked potential with increasing pacing amplitude in permanent bipolar pacing leads.

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Effect of Quinidine or Procainamide Versus No Antiarrhythmic Drug on Sudden Cardiac Death, Total Cardiac Death, and Total Death in Elderly Patients with Heart Disease and Complex Ventricular Arrhythmias

Wilbert S. Aronow, Anthony D. Mercado, Stanley Epstein, and Itzhak Kronzon

What is the effect of quinidine or procainamide versus no antiarrhythmic drug on sudden, cardiac and total death? In 406 elderly patients with heart disease and asymptomatic complex ventricular arrhythmias, survival by Kaplan-Meier analysis showed no significant difference between the 2 groups for sudden, cardiac, or total death through 4 years.

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Balloon Angioplasty for Congenital Mitral Stenosis

Philip J. Spevak, John L. Bass, Giora Ben-Shachar, Peter Hesslein, John F. Keane, Stan Perry, Lee Pyles, and James E. Lock

We attempted balloon angioplasty in 9 children with congenital mitral stenosis who were symptomatic with severe congestive heart failure. Effective reduction in mitral gradient was initially achieved in 7 patients. No strokes, infections or deaths were due to the procedure. Balloon angioplasty should be considered before mitral valve replacement in younger patients and in those whose mitral valve replacement would be problematic.

MISCELLANEOUS

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Effects of Plasma Volume Expansion on Hemodynamics and Atrial Natriuretic Factor Release in Heart-Transplant Recipients

Jean-Claude Dussaule, Alain Nitenberg, Oscar Tavoraro, Christophe Benvenuti, Daniel Loisan, Alain Castaigne, Jean-Paul Cachera, and Raymond Ardaillou

Plasma atrial natriuretic factor, plasma cyclic guanosine monophosphate, plasma aldosterone, plasma-renin activity and hemodynamic parameters were measured in heart-transplant recipients and control patients (chest pain syndrome) during right-sided heart catheterization under basal conditions and in response to an intravenous saline load. Basal plasma ANF and cGMP were higher in heart-transplant recipients than in control patients, whereas PRA and plasma aldosterone did not differ. The sluggish response of plasma ANF in this group was associated in the postinfusion period with a nonreturn of the hemodynamic parameters to their basal values in contrast with what was observed in control patients.

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Improved Prediction of Left Ventricular Mass by Regression Analysis of Body Surface Potential Maps

Fred Kornreich, Terrence J. Montague, Gerard van Herpen, Pentti M. Rautaharju, Philippe Smets, and Michèle Dramaix

In 72 normal subjects and 84 patients with left ventricular hypertrophy, we recorded body surface potential maps from 117 thoracic sites and 3 limb electrodes. Substantial improvement in predicting LV mass from electrocardiographic measurements can be achieved by appropriate selection of a limited, practical subset of electrode positions from body surface potential maps.

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Noninvasive Estimation of Right Atrial Pressure from the Inspiratory Collapse of the Inferior Vena Cava

Barbara J. Kircher, Ronald B. Himelman, and Nelson S. Schiller

The percent respiratory collapse of the inferior vena cava on 2-dimensional echocardiography was compared to right atrial pressure determined by flotation catheter within 24 hours of echo in 83 patients. Sensitivity and specificity for discriminating right atrial pressure \leq or ≥ 10 mm Hg was maximized at the 50% level of inferior vena cava collapse. Two-dimensional echocardiography can be used as a simple guide to right atrial pressure.

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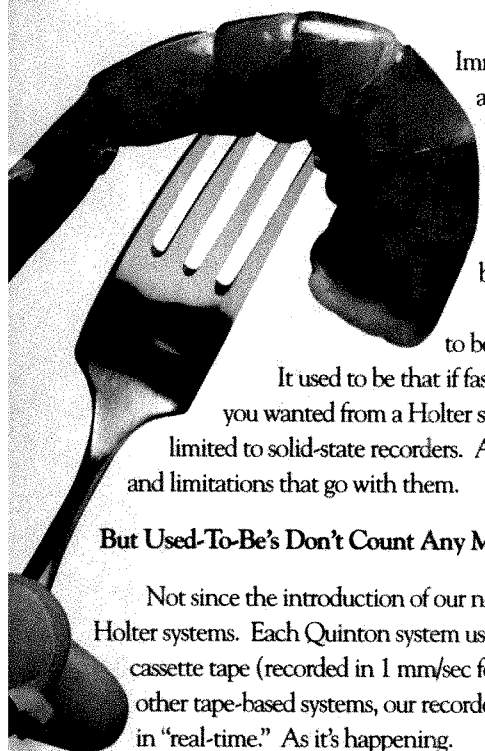
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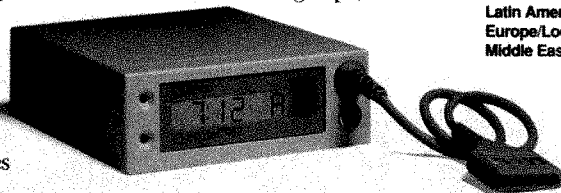
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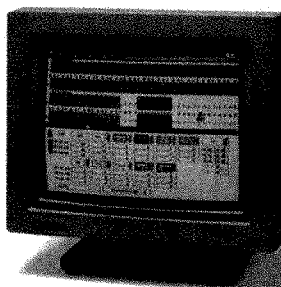
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389**ST Monitoring for Myocardial Ischemia During and After Coronary Angioplasty**

Masahiro Mizutani, S. Ben Freedman, Elizabeth Barns, Sadamasa Ogasawara, Brian P. Bailey, and Louis Bernstein

We performed 12-lead electrocardiographic monitoring in 97 patients during PTCA. Ischemia (pain or ST change) occurred in 80%, but only in 65% of those with collaterals. Ischemia was more common in left anterior descending and left circumflex than right coronary PTCA, but pain was the only manifestation more commonly in left circumflex and right coronary than left anterior descending PTCA. Patients with ischemia during inflation had less severe lesions, higher transstenotic gradients and lower distal occluded pressure than those without ischemia. The best combination of 3 leads to detect ischemia during inflation was V₃/III/V₅ for left anterior descending PTCA and III/V₂/V₅ for left circumflex and right coronary artery PTCA, giving a sensitivity of 100% compared to all 12 leads. In 50 of the patients monitored for 20 hours after PTCA, recurrent ST elevation was detected in 2 (4%) and preceded chest pain in both. Thus, ST changes during PTCA may be reliably detected by optimal selection of 3 leads. Occurrence of ischemia is related principally to the vessel dilated and lesion hemodynamics. Recurrent ischemia is uncommon immediately after PTCA and may be detected by single-lead ST monitoring.

394**Value of Thallium-201 ReInjection After Delayed SPECT Imaging for Predicting Reversible Ischemia After Coronary Artery Bypass Grafting**

Hiroshi Ohtani, Nagara Tamaki, Yoshiharu Yonekura, Ishtiaque H. Mohiuddin, Kazuo Hirata, Toshihiko Ban, and Junji Konishi

Predictive value of preoperative reinjection thallium-201 imaging for improvement in regional function after coronary artery bypass grafting (CABG) was evaluated. After routine stress and 3-hour delayed imaging, 40 MBq of thallium-201 was injected to perform the reinjection tomography in 24 patients before the operation. New redistribution was obtained after reinjection in 47% of the segments without definite redistribution on the delayed images. Among the segments without redistribution on the delayed images, postoperative improvement in perfusion and wall motion was observed more often in the segments exhibiting the new redistribution

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than those without redistribution after reinjection. The predictive values for such improvement were higher by the reinjection imaging than those by the delayed imaging. Thus, the reinjection of thallium-201 should be performed to identify reversible ischemic segments after CABG when routine stress and delayed imaging show no redistribution.

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Preservation of Left Ventricular Performance with Reduced Ischemic Dysfunction by Intravenous Nisoldipine

Brian P. Kimball, K. Randal Watson, Sanh Bui, and David Frankel

The effect of intravenous nisoldipine on cardiac performance was examined during pacing-induced ischemia in 14 patients with coronary artery disease. The relative contributions of afterload decrease or prevention of myocardial ischemia were assessed using load-independent global (peak-systolic pressure/end-systolic volume) and regional (peak-systolic pressure/end-systolic radial length) "contractile" indexes. Nisoldipine decreased aortic pressure and prevented elevation of left ventricular end-diastolic pressure during rapid atrial pacing. Resting cardiac index and left ventricular ejection fraction increased after nisoldipine, which also prevented the deterioration in left ventricular ejection fraction and fractional radial shortening during rapid atrial pacing. Under these conditions, nisoldipine preserved myocardial function, as determined by global peak systolic pressure/end-systolic volume and regional "contractile" indexes. Intravenous nisoldipine maintains ventricular performance during rapid atrial pacing via a combination of systemic vasodilation and amelioration of ischemic myocardial dysfunction.

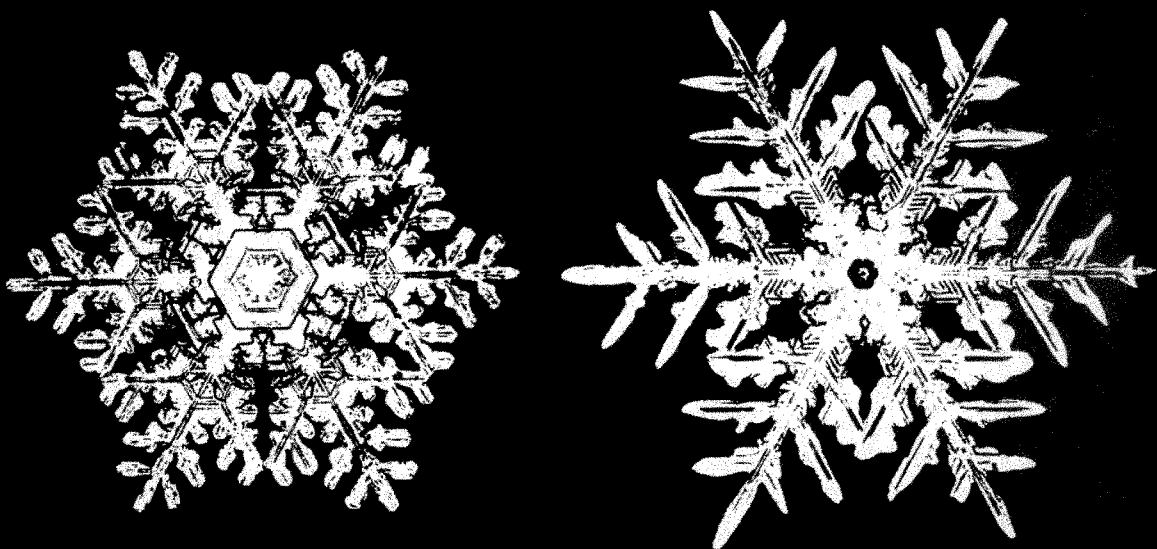
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Usefulness of Semiquantitative Analysis of Dipyridamole-Thallium-201 Redistribution for Improving Risk Stratification Before Vascular Surgery

John R. Levinson, Charles A. Boucher, Christopher M. Coley, Timothy E. Guiney, H. William Strauss, and Kim A. Eagle

Dipyridamole-thallium-201 scanning is sensitive in identifying patients prone to ischemic cardiac complications after vascular surgery, but its specificity is limited. To determine which patients with redistribution are at highest risk, thallium images were interpreted semiquantitatively in 62 consecutive patients. Each scan was analyzed for the number of myocardial segments, the number of thallium views and the number of coronary artery territories with redistribution. Seventeen patients (27%) had post-operative events, including unstable angina pectoris, ischemic pulmonary edema, myocardial infarction and cardiac death. Thallium predictors of these events included redistribution in ≥ 4 segments ($p = 0.03$), ≥ 2 segments ($p = 0.005$) and ≥ 2 coronary territories ($p = 0.007$). No patient with redistribution in only 1 view had an ischemic event (0 of 15). Thus, determining the extent of redistribution by dipyridamole-thallium-201 scanning improves risk stratification before vascular surgery.

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Management of Complications Associated with a First-Generation Endocardial Defibrillation Lead System for Implantable Cardioverter-Defibrillators

Nicholas G. Tullo, Sanjeev Saxena, Ryszard B. Krol, Ann Marie Mauro, Denise Kunecz

An automatic cardioverter-defibrillator was implanted using an endocardial defibrillation lead system in 10 patients with sustained ventricular tachycardia or ventricular defibrillation. Six lead system complications were observed during a follow-up period of 51 ± 36 weeks. Three catheter electrode fractures occurred, and 2 patch electrode fractures were detected. Lead fracture was often asymptomatic, but 1 patient presented with inappropriate defibrillator shocks and 1 patient died suddenly. One additional complication involved malfunction of a previously implanted permanent pacemaker pulse generator during defibrillator threshold testing. Catheter and patch electrode replacement procedures were performed in 3 patients. It is concluded that serial clinical, roentgenographic and electrophysiologic evaluation should be included in follow-up procedures for endocardial defibrillation lead systems. Endocardial defibrillation threshold testing may cause malfunction of previously implanted pacemaker systems. Endocardial lead replacement is feasible without thoracotomy.

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Characteristic Variation in Evoked Potential Amplitude with Changes in Pacing Stimulus Strength

Anne B. Curtis, Fred Vance, and Kim Miller-Shifrin

Using a computer-based pacing system emulator, stimuli at various amplitudes were delivered to 12 patients through permanent bipolar pacing leads with measurement of the amplitude of the resultant evoked potentials. Evoked potential amplitude declined significantly as stimulus amplitude increased. Pacing at 2.5 V was performed in an additional 8 patients with temporary quadripolar electrode catheters. Evoked potential amplitude was maximal when the proximal 3 poles of the catheter were connected as a common anode. When the proximal 2 poles of the catheter were disconnected to make the anode equal in size and current density to the cathode, the evoked potential again declined significantly. The decline in evoked potential amplitude at high stimulus amplitudes in permanent pacing leads can be reproduced by manipulation of the size and current density of the anode of temporary electrode catheters, suggesting that anodal stimulation at the ring of permanent pacing leads may be responsible.

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423**Effect of Quinidine or Procainamide Versus No Antiarrhythmic Drug on Sudden Cardiac Death, Total Cardiac Death, and Total Death in Elderly Patients with Heart Disease and Complex Ventricular Arrhythmias**

Wilbert S. Aronow, Anthony D. Mercado, Stanley Epstein, and Itzhak Kronzon

A prospective study correlated the effect of quinidine or procainamide versus no antiarrhythmic drug on sudden, cardiac and total death in 406 elderly patients with heart disease and asymptomatic complex ventricular arrhythmias. Of 397 patients treated with quinidine, 184 (46%) developed adverse effects during the first 2 weeks of therapy and were given no further antiarrhythmic therapy. Of 9 patients treated with procainamide, 2 (22%) developed adverse effects during the first 2 weeks of therapy and were given no further antiarrhythmic therapy. Mean follow-up was 24 ± 15 months in both groups. Sudden, cardiac and total death occurred in 21, 43 and 65% of patients receiving quinidine or procainamide, respectively, and in 23, 44 and 63% of patients receiving no antiarrhythmic drug, respectively (difference not significant). Survival by Kaplan-Meier analysis showed no significant difference between the 2 groups for sudden, cardiac or total death through 4 years.

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435**Vasodilators Have Not Been Shown to Be of Value in All Patients with Chronic Congestive Heart Failure Due to Left Ventricular Systolic Dysfunction**

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439**All Patients with Left Ventricular Systolic Dysfunction Should Be Treated with An Angiotensin-Converting Enzyme Inhibitor: A Protagonist's Viewpoint**

Barry M. Massie

444**Nitrates Are Effective in the Treatment of Chronic Congestive Heart Failure: The Protagonist's View**

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CONGENITAL HEART DISEASE

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Balloon Angioplasty for Congenital Mitral Stenosis

Philip J. Spevak, John L. Bass, Giora Ben-Shachar, Peter Hesslein, John F. Keane, Stan Perry, Lee Pyles, and James E. Lock

Balloon angioplasty was attempted in 9 children (aged 0.1 to 10 years) with congenital mitral stenosis (MS). All were symptomatic with severe congestive failure and failure to thrive. Effective reduction in mitral gradient was initially achieved in 7 patients. For the entire group, the mean valve gradient decreased from 14.8 ± 5.0 to 8.1 ± 6.7 mm ($p = 0.0007$) and mean valve area increased from 1.1 ± 0.5 to 1.8 ± 0.9 cm²/m² ($p = 0.003$). More than mild mitral regurgitation developed in 2 patients but none required surgery for mitral regurgitation. Poor gradient relief followed dilation of valves with unbalanced chordal attachments, with restriction to the valve apparatus as in mitral arcade, and when the obstruction was not purely valvar as with a supramitral ring. No strokes, infections or deaths were due to the procedure. Based on these data, balloon angioplasty of congenital MS should be considered before mitral valve replacement in younger patients and in those in whom mitral valve replacement would be problematic.

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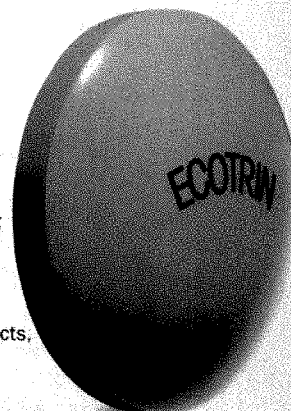
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References: 1. Faigel DJ, Jakubowski JA, Stampfer MJ, et al: Multiple doses of regular and enteric-coated aspirin produce equivalent platelet inhibitory effects. *Curr Ther Res* 1986; 39:519-527.

2. Demke DM, Luderer JR, Wakefield KL, et al: The effect of itazigrel and aspirin on the mucosa of the esophagus, stomach, and duodenum of normal subjects. *J Clin Pharmacol* 1987; 27: 916-920.

3. Data on file, SmithKline Consumer Products, a SmithKline Beechman Company.

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MISCELLANEOUS**477****Effects of Plasma Volume Expansion on Hemodynamics and Atrial Natriuretic Factor Release in Heart-Transplant Recipients**

Jean-Claude Dussaule, Alain Nitenberg, Oscar Tavoraro, Christophe Benvenuti, Daniel Loisan, Alain Castaigne, Jean-Paul Cachera, and Raymond Ardaillou

Basal plasma atrial natriuretic factor (ANF) and cyclic guanosine monophosphate were higher in heart-transplant recipients than in control patients. These high values appeared to be related to elevated atrial dimensions and cyclosporine-induced renal failure. During volume expansion, the changes in plasma ANF were less marked in heart-transplant recipients than in control patients despite identical increases of atrial pressures. The sluggish response of plasma ANF in the first group was associated in the postinfusion period with a nonreturn of the hemodynamic parameters to their basal values.

METHODS**485****Improved Prediction of Left Ventricular Mass by Regression Analysis of Body Surface Potential Maps**

Fred Kornreich, Terrence J. Montague, Gerard van Herpen, Pentti M. Rautaharju, Philippe Smets, and Michèle Dramaix

Body surface potential maps were recorded from 117 thoracic sites and 3 limb electrodes in 72 normal subjects and 84 patients with left ventricular (LV) hypertrophy. Multiple regression analysis was performed separately for 54 women and 102 men on 120-lead data, using as features instantaneous voltages on time-normalized P, PR, QRS and ST-T waveforms. Leads and features for optimal prediction of echocardiographically determined LV mass were selected. A total of 6 features from 3 torso sites in men and from the same 3 sites plus 2 others in women yielded correlations between echocardiographic and electrocardiographic estimates of LV mass of 0.89 and 0.88, respectively. The standard errors of the estimate (SEE) were 31 and 22 g, respectively. The single most potent predictor in both sexes was a mid-QRS voltage measured on a lead positioned 10 cm below V₁; QRS duration, late QRS and early-to-mid T wave amplitudes recorded in the lower left flank contributed significantly to the performance of both regression models. In comparison, regression analysis on the standard 12-lead electrocardiogram in the same population produced a correlation of 0.76 in men and 0.75 in women; the SEE were 48 and 35 g, respectively.

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Noninvasive Estimation of Right Atrial Pressure from the Inspiratory Collapse of the Inferior Vena Cava

Barbara J. Kircher, Ronald B. Himelman, and Nelson S. Schiller

The percent respiratory collapse of the inferior vena cava on 2-dimensional echocardiography was compared to right atrial pressure determined by flotation catheter within 24 hours of echo in 83 patients. Sensitivity and specificity for discriminating right atrial pressure \leq or \geq 10 mm Hg was maximized at the 50% level of inferior vena cava collapse. Two-dimensional echocardiography can be used as a simple guide to right atrial pressure.

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Autonomic Nervous System Activity During Myocardial Ischemia in Man Estimated by Power Spectral Analysis of Heart Period Variability

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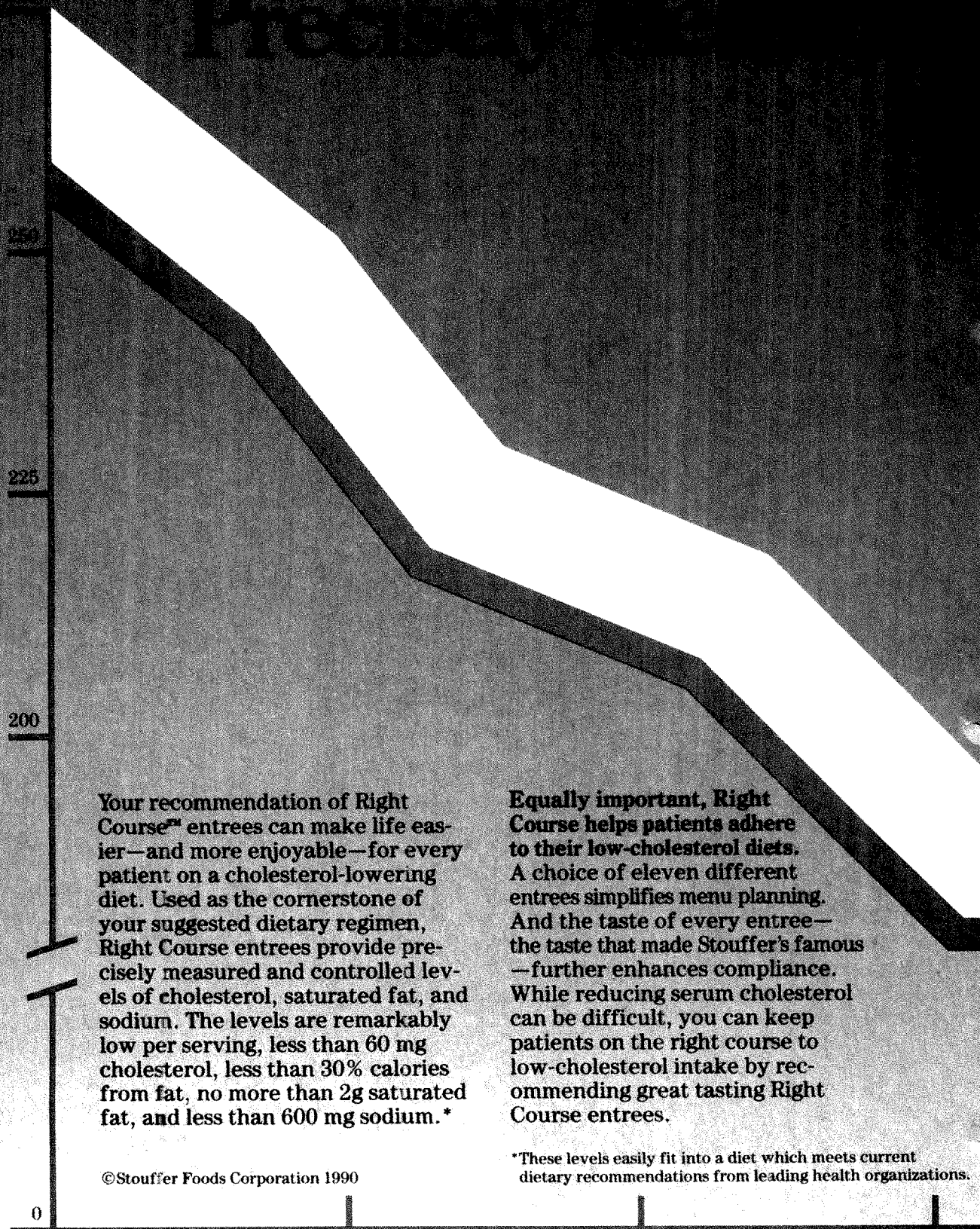
The Probability of Detecting a Subaortic Ridge in Children with Ventricular Septal Defect or Coarctation of the Aorta

Steven C. Cassidy, George F. Van Hare, and Norman H. Silverman

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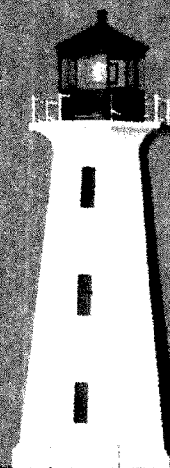
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ST Monitoring for Myocardial Ischemia During and After Coronary Angioplasty

Masahiro Mizutani, MD, S. Ben Freedman, MB, PhD, Elizabeth Barns, SRN, Sadamasa Ogasawara, MD, Brian P. Bailey, MB, and Louis Bernstein, MB

We performed 12-lead electrocardiographic monitoring in 97 patients during coronary angioplasty (PTCA) of a single vessel to correlate ischemic ST changes with clinical, angiographic and coronary hemodynamic variables and to determine the optimum lead or combination of leads for their detection. Ischemia (chest pain or ST change, group A) occurred in 79 patients (80%), but in only 15 of 23 patients (65%) with collaterals ($p < 0.05$). Ischemia occurred more often in left anterior descending and left circumflex PTCA than right coronary PTCA, but pain was the only manifestation more often in left circumflex and right coronary PTCA. Ischemic ST change was silent in 16% and this proportion did not differ in clinical or angiographic groups except for diabetes with 3 of 5 (60%) having silent ischemia ($p < 0.05$). Patients in group A (ischemia) compared to group B (no ischemia) had less severe lesions (85 ± 9 vs $91 \pm 7\%$, $p < 0.01$), higher transstenotic gradients (62 ± 19 vs 53 ± 9 mm Hg, $p < 0.05$) and lower distal occluded pressures (24 ± 11 vs 33 ± 10 mm Hg, $p < 0.01$), suggesting less collateral flow. Compared with a 12-lead electrocardiogram, the best single lead for detecting ST change during PTCA in each artery had a sensitivity of 80% and this increased to 93% using the best 2 leads. The best 3 leads ($V_3/III/V_5$ for left anterior descending and $III/V_2/V_5$ for right coronary and left circumflex) increased sensitivity to 100%. In 50 of the patients, the lead showing maximum ST change during PTCA was monitored for a mean of 20 hours after PTCA. Recurrent ST change occurred in 2 patients (4%), both with ST \uparrow , which preceded chest pain in both. Thus, ST changes during PTCA may be reliably detected by optimal choice of 3 electrocardiographic leads. The occurrence of ischemia is related principally to the vessel dilated and lesion hemodynamics that proba-

bly reflect collateral flow. Recurrent ischemia after PTCA is uncommon and may be detected by ST monitoring of a single lead.

(Am J Cardiol 1990;66:389-393)

Monitoring for ischemia during percutaneous transluminal coronary angiography (PTCA) is performed routinely in most laboratories using from 1 to 3 arbitrarily chosen electrocardiographic leads to detect ST-segment change. Although it is generally accepted that 12-lead electrocardiographic monitoring is more sensitive than monitoring only 1 to 3 leads,¹⁻³ most comparisons have not used leads optimally selected for each artery. Continuous monitoring of the electrocardiogram has also been advocated in the period immediately after PTCA to detect ischemic events that may be silent^{1,4} and which have been reported to occur with an incidence varying between 7 and 23%.^{1,4} In this study, we performed 12-lead monitoring during PTCA to correlate ischemic ST changes with clinical, angiographic and coronary hemodynamic variables and to select the optimum leads or lead combinations for detection of ischemic ST change. In a subset with ischemic ST changes during PTCA, we also monitored the electrocardiogram after PTCA to determine the incidence of recurrent ischemic events.

METHODS

Patients: We studied 108 consecutive patients undergoing PTCA of 1 coronary artery for angina pectoris. Of these, 11 were excluded (2 with lesions not crossed by the balloon, 3 with left bundle branch block and 6 with inadequate electrocardiograms). The remaining 97 underwent PTCA and electrocardiographic recordings as described below. There were 71 men and 26 women in the study, with a mean age of 55 ± 9 years (range 33 to 75). The clinical indication for PTCA was stable effort angina in 35 patients and unstable angina in 62 patients. There was a history of infarction in 36 patients (anterior in 19 and inferior in 17). In 21 patients, this was a Q-wave infarction and in 15, a non-Q-wave infarction. Seven had undergone prior bypass surgery and 9 were diabetic.

Angiography before PTCA revealed 1-vessel disease ($\geq 70\%$ luminal diameter decrease) in 73 patients and multivessel disease in 24. Collateral flow was demon-

From the Hallstrom Institute of Cardiology, University of Sydney, and Royal Prince Alfred Hospital, Sydney, Australia. This study was supported in part by grants from the National Health and Medical Research Council of Australia, and the Postgraduate Foundation of the University of Sydney. Manuscript received December 27, 1989; revised manuscript received and accepted April 9, 1990.

Address for reprints: S.B. Freedman, MB, PhD, Hallstrom Institute of Cardiology, Royal Prince Alfred Hospital, Missenden Road, Camperdown NSW 2050, Sydney, Australia.

strable in 23. The mean left ventricular ejection fraction was $67 \pm 10\%$ (range 46 to 86). The left anterior descending coronary artery was dilated in 38 patients, left circumflex in 28 and right coronary artery in 31. Another 28 patients (test set) underwent 12-lead recordings during PTCA to determine prospectively the accuracy of electrocardiographic lead selection derived from the 97 patients described above (learning set). The 28 patients comprised 25 men and 3 women, with a mean age 55 ± 8 years, including 21 with left anterior descending, 2 with left circumflex and 5 with right coronary dilatations.

Angioplasty technique: PTCA was performed by the transfemoral approach, using standard techniques. Patients were pretreated with oral aspirin and dipyridamole and intravenous heparin. Measurement of lesion hemodynamics was possible in 77 patients in whom the dilatation balloon had a distal pressure monitoring port. We recorded the transstenotic pressure gradient before, and the distal occluded pressure during the initial balloon inflation.

Electrocardiographic recordings and angiography: A 12-lead electrocardiogram was recorded at 10-second

intervals before and during each inflation using a 3-channel Avionics recorder and radiolucent carbon-fibre electrodes and leads. Significant ST-segment change was defined as ≥ 1 mm elevation or depression of the ST segment measured 60 ms after the J point, relative to the TP segment. Measurements were made at the point of maximal ST-segment change. Coronary angiograms were reviewed by at least 2 observers blinded to the electrocardiographic data. The number and the severity (percent luminal diameter decrease) of coronary stenoses were determined by visual inspection.

ST monitoring after angioplasty: In 50 of the patients with ST elevation during PTCA, the lead showing maximum ST elevation was monitored for a mean of 20 hours after PTCA using a single-channel ST monitor we have previously validated.⁵ This monitor produces an alarm and a short electrocardiogram strip for verification, as well as a continuous trend plot of the ST-segment level against time.

Statistical analysis: Results were expressed as mean \pm standard deviation. The unpaired *t* test was used to examine significance of group mean differences and the exact conditional binomial probability test (as appropriate).

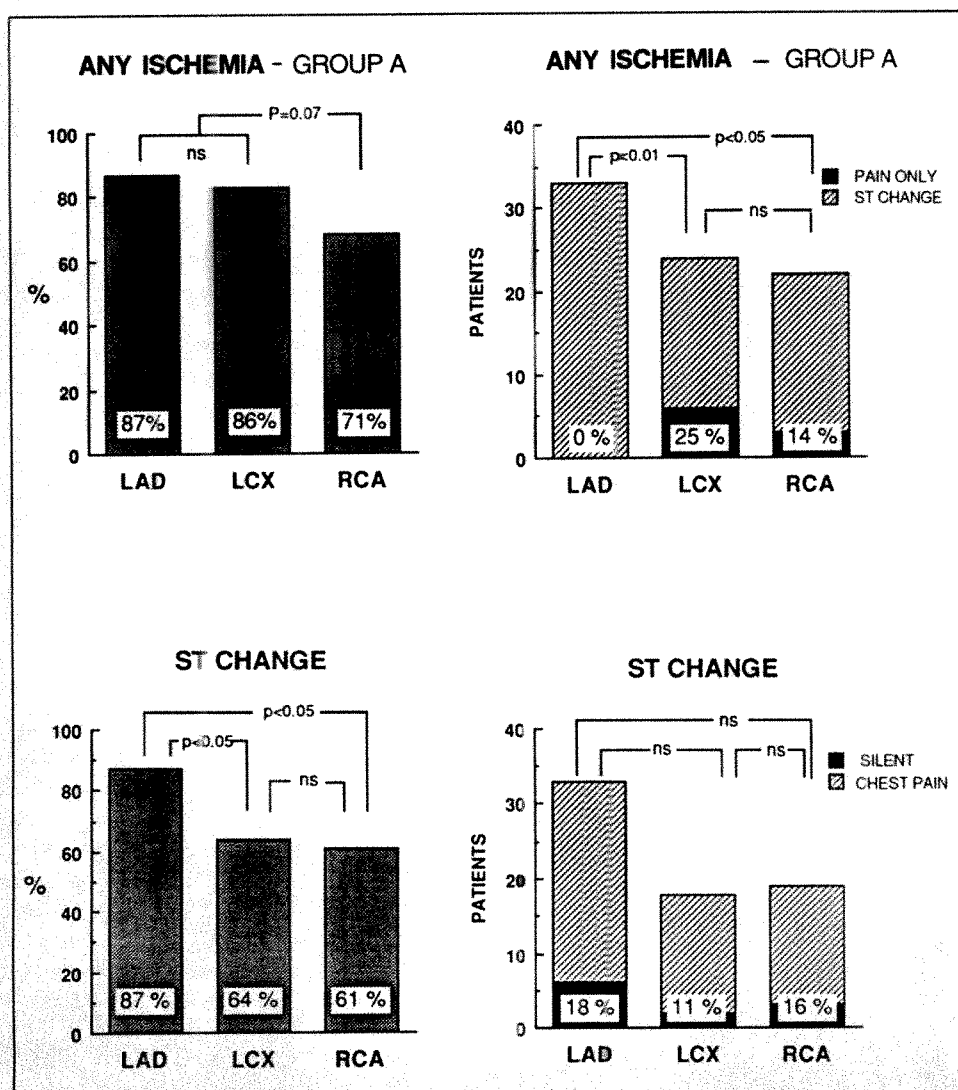


FIGURE 1. Relation of vessel dilated to ischemia during percutaneous transluminal coronary angioplasty (PTCA). *Top left* shows proportion of patients developing ischemia (ST change or pain, group A) during PTCA. *Top right* shows proportion of group A patients in whom pain was the only manifestation of ischemia (solid portion). *Bottom left* shows proportion with ST change during PTCA and *bottom right* shows proportion with ST change in whom this was silent. LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; ns = not significant.

TABLE I Clinical and Angiographic Correlations with Ischemia During Angioplasty

	n	Group A Any Ischemia (%)	Group B No Ischemia (%)	p Value
Stable angina	35	29 (83)	6 (17)	NS
Unstable angina	62	50 (81)	12 (19)	NS
Q-wave MI	21	16 (76)	5 (24)	NS
Non-Q-wave MI	15	14 (93)	1 (7)	NS
No MI	61	49 (80)	12 (20)	NS
Prior CABG	7	7 (100)	0 (0)	NS
Diabetic	9	5 (56)	4 (44)	NS
1-vessel CAD	73	57 (78)	16 (22)	NS
Multivessel CAD	24	22 (92)	2 (8)	NS
Collaterals present	23	15 (65)	8 (35)	<0.05
Proximal narrowing	26	23 (88)	3 (12)	NS
Distal narrowing	71	56 (79)	15 (21)	NS
Overall	97	79 (80)	18 (20)	

CABG = coronary artery bypass grafting; CAD = coronary artery disease; MI = myocardial infarction; NS = not significant.

ate for samples with small expected cell sizes) was used to assess differences of proportions.⁶ A p value (2-tailed) <0.05 was considered significant.

RESULTS

Clinical, angiographic and hemodynamic correlations with ischemia: Patients were divided into 2 groups based on evidence of ischemia during PTCA. Group A comprised 79 patients (80%) with some evidence of ischemia during balloon inflation, that is, either ST elevation or depression or chest pain or both, while group B comprised 18 patients (20%) with neither chest pain nor ischemic ST changes. Of the 79 group A patients, 59 had both chest pain and ischemic ST changes, 9 had chest pain only and 11 had ST changes only (silent ischemia). The mean age of group A patients was not different from group B patients (57 ± 9 versus 52 ± 9 years, respectively). The mean duration of balloon inflation was greater in group B than in group A (89 ± 39 versus 55 ± 29 seconds, $p < 0.01$) because inflations were maintained longer when there were no ST changes or chest pain.

The proportion of patients in the different clinical and angiographic subsets showing some evidence of ischemia during PTCA (group A) is listed in Table I. There were no significant differences for any of the clinical subsets, although numbers in some of the subsets were small and a real difference cannot be excluded. As might be expected, ischemia was less frequent in patients with collaterals.

The relation of the vessel dilated to ischemia during PTCA is shown in Figure 1. Some evidence of ischemia (ST change or pain, group A) was more likely to occur with left anterior descending or circumflex inflations than right coronary artery inflations ($p = 0.07$, Figure 1). Pain was the only manifestation of ischemia more frequently in either left circumflex or right coronary than in left anterior descending inflations, where this was never observed (Figure 1). ST changes during PTCA occurred more frequently with left anterior descending inflations than with either left circumflex or

TABLE II Correlation Between Angiographic Severity, Lesion Hemodynamics and Ischemia During Angioplasty

	Any Ischemia Group A	No Ischemia Group B	p Value
Mean %	85 ± 9	91 ± 7	<0.01
Stenosis	(n = 79)	(n = 18)	
Transstenotic gradient (mm Hg)	62 ± 19	53 ± 9	<0.05
	(n = 65)	(n = 12)	
Distal occluded pressure (mm Hg)	24 ± 11	33 ± 10	<0.01
	(n = 65)	(n = 12)	

TABLE III Electrocardiographic Changes and Duration of Inflation in Silent and Symptomatic Ischemia

	Symptomatic	Silent	p Value
Σ ST \uparrow (mm)	6.6 ± 8.0	4.5 ± 4.9	NS
Σ ST Δ (mm)	9.7 ± 8.7	6.1 ± 5.7	NS
No. of leads with ST \uparrow	3.1 ± 2.1	2.9 ± 2.2	NS
No. of leads with ST Δ	5.4 ± 2.7	4.5 ± 2.9	NS
Duration of inflation (s)	54 ± 15	50 ± 18	NS

NS = not significant; Σ ST \uparrow = Sum of ST segment elevation; Σ ST Δ = sum of ST segment deviation (elevation or depression).

right coronary inflations (Figure 1), but the proportion of inflations with ischemic ST changes that were silent (i.e., no pain) was similar in all 3 arteries (Figure 1).

The correlations between ischemia during PTCA and lesion severity and hemodynamics are listed in Table II. The group with some evidence of ischemia (pain or ST changes, group A) had a slightly lower mean percent stenosis than Group B, with a higher mean transstenotic gradient and lower distal occluded pressure, probably reflecting differences in effective collateral flow.

ST-segment change occurred during PTCA in 70 patients, and in 11 (16%) this was not accompanied by pain (silent ischemia). This proportion was not different in any clinical or angiographic subset except for diabetes, where 3 of the 5 diabetic patients with ischemia during PTCA (60%) had silent ischemia ($p < 0.05$). The duration of inflation was not different in silent and symptomatic ischemia and while ST changes tended to be greater in symptomatic episodes, the differences were not significant (Table III).

Sensitivity of individual leads for detecting ischemia: In the 70 patients with ischemic change (ST elevation and/or depression ≥ 1 mm), the frequency of ST deviation in individual leads is listed in Table IV, for each coronary artery. The most sensitive lead for detecting ST elevation was V_2 or V_3 for the left anterior descending, lead III for left circumflex and lead III or aVF for right coronary artery. The most sensitive lead for detecting ST depression was lead III for left anterior descending, V_2 or V_3 for left circumflex and V_2 for right coronary artery. The lead that most often showed the maximum ST elevation was V_3 for the left anterior descending and lead III or aVF for left circumflex and right coronary artery, while the lead most often showing maximum ST depression was lead III for the left anteri-

TABLE IV ST Changes in Individual Electrocardiographic Leads During Angioplasty

Lead	ST Elevation			ST Depression		
	LAD	LC	RIGHT	LAD	LC	RIGHT
I	5	0	0	0	1	3
II	2	7	12	12	1	1
III	1	8	14	14	1	2
aVL	8	0	0	2	3	9
aVF	1	7	14	13	1	1
V ₁	17	0	1	1	5	2
V ₂	30	0	2	1	12	8
V ₃	30	0	2	3	12	7
V ₄	24	0	2	5	6	6
V ₅	13	1	0	5	6	5
V ₆	8	4	0	4	3	3
Any lead	30	8	16	16	17	15

Numbers in the table refer to numbers of patients with ST elevation or depression in that lead.
LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; Right = right coronary artery.

TABLE V Performance of Best Individual Lead or Combination of Leads for Detecting ST Deviation During Angioplasty

	LAD n = 33	LC n = 18	Right n = 19
1 lead			
Lead	V ₃	III	III
No. detected (sensitivity %)	31 (94)	9 (50)	16 (84)
No. failures	0	0	0
2 leads			
Leads	V ₃ /III	III/V ₂	III/V ₂
No. detected (sensitivity %)	32 (97)	15 (83)	18 (95)
No. failures	1	0	0
3 leads			
Lead	V ₃ /III/V ₅	III/V ₂ /V ₅	III/V ₂ /V ₅
No. detected (sensitivity %)	33 (100)	18 (100)	19 (100)
No. failures	1	0	0

Failure = failure to show ST elevation occurring in another lead when the lead group detected ST depression; LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; Right = right coronary artery.

or descending and V₂ for the left circumflex and right coronary artery.

The ability of a lead or combination of leads to detect ischemia was expressed as sensitivity for detection of ST deviation (elevation or depression) compared to all 12 leads. When a lead or combination of leads detected ST depression but failed to show ST elevation that occurred in another lead, this was recorded as a failure (to show ST elevation). Using the sensitivity, number of failures and magnitude of ST change to select leads or lead groups, the best single lead and combination of 2 or 3 leads for detecting ischemia during PTCA of each artery are listed in Table V. Selecting the best single lead for monitoring in each artery would have resulted in an overall sensitivity of only 80% for detecting ST deviation, with no failures. Using the best combination of 2 leads for each artery, the overall sensitivity increased to 93%, with a 1% failure rate, while the best combination of 3 leads for each artery gave 100% sensitivity for detecting ischemia, with a 1% failure rate. This failure was in a patient with left anterior descending disease, who showed ST elevation in lead I and aVL and ST depression in V₃.

Test set: When these combinations of 2 or 3 leads derived from the 97-patient learning set were prospectively applied to the test set of 28 patients, the best combination of 2 or 3 leads gave a sensitivity of 100% with 1 failure for 2 leads and no failures for 3 leads, that is, an accuracy almost identical to that seen in the learning set.

Monitoring after angioplasty: In 50 of the patients with ischemic ST change during balloon inflation, the lead showing maximum ST-segment deviation was monitored in the coronary care unit for a mean of 20 hours after PTCA. Recurrent ischemic ST change was detected in 2 patients, both with ST elevation. The ST-segment elevation preceded chest pain in both patients and, in 1, resulted in referral for urgent bypass surgery. The other patient was not revascularized and had a limited infarction.

DISCUSSION

The incidence of ischemia during PTCA as judged by ST deviation or pain did not vary significantly between the different clinical subsets, although patients with collaterals were less likely to develop ischemia. The protective effect of collaterals may be underestimated, because they can be recruited during balloon inflation as shown by simultaneous injection of the contralateral artery.⁷ Meier et al⁷ showed that coronary wedge or distal occluded pressure was higher in patients with visible or recruitable collaterals and suggested a pressure ≥ 30 mm Hg may be a good marker of physiologically significant collateral flow. This is supported by our findings of greater mean distal occluded pressure (33 versus 24 mm Hg) and lower transstenotic pressure gradient in group B patients without evidence of ischemia. In addition, we found that mean stenosis severity in patients without ischemia during PTCA was 91%, which was significantly greater than in group A patients (85%). While these differences are small, they may be important for development of collaterals, which are usually not visible with lesions $<90\%$ in patients with 1-vessel coronary disease.⁸

Although ischemia (pain and/or ST segment changes) occurred with equal frequency in left anterior descending and circumflex occlusions, pain as the only manifestation of ischemia was significantly more frequent in the left circumflex artery. This is compatible with previous data indicating that transmural ischemia in the distribution of the left circumflex artery is likely to be 'electrocardiographically silent'.⁹ It is unlikely that this is due to a lower incidence of ischemia, as the incidence of ischemia (pain or ST changes) was equal in left anterior descending and circumflex occlusions. Also, in a previous study, a simultaneously recorded intracoronary electrogram showed transmural ischemia at times when the 12-lead electrocardiogram showed no significant ST shift.⁹ This electrocardiographic 'silence' is probably related to geometry and positioning of the 12 leads in relation to the posterolateral left ventricular

wall, which becomes ischemic during left circumflex occlusions.^{9,10}

Ischemia was silent in 16% of our patients and the proportion did not differ between clinical or angiographic subgroups. There was a tendency for symptomatic ischemia to show greater ST-segment deviation than silent ischemia, but there was an enormous overlap, as previously shown in other studies of silent ischemia.¹¹ Although patient numbers were too small to draw firm conclusions, diabetics were more likely to show silent ischemia during balloon inflation, consistent with previous reports of an increased incidence of silent ischemia and infarction in diabetics.^{12,13}

Although 12-lead monitoring during PTCA should provide optimum sensitivity for detection of ischemia, most laboratories use between 1 and 3 leads. Previous studies have suggested an inadequate sensitivity of 2 or 3 leads for detecting ischemia,¹⁻³ but in those studies, the 2 or 3 leads chosen were either fixed for all 3 coronary arteries or picked arbitrarily without consideration of which lead or combination of leads was best for each individual artery. In this study, we selected the best single lead and combination of 2 and 3 leads for each artery based on a comparison of performance with the 12-lead electrocardiogram. Our results indicate that use of a single lead is inadequate, but by using 2 appropriate leads, an overall sensitivity of 93% can be achieved with a very low failure rate. Addition of a third lead increases sensitivity to 100%, indicating these 3 leads could replace the 12-lead electrocardiogram for monitoring during PTCA. In laboratories with only 2 monitoring leads, appropriate lead selection for each artery should provide adequate accuracy for clinical purposes.

Because lesions in arteries that have been dilated may be unstable and can occlude with either vasospasm, thrombus or dissection, it would seem logical to monitor patients for recurrence of ischemia in the immediate postangioplasty period. Krucoff et al^{1,14} have shown that the 12-lead electrocardiographic appearance during occlusion is closely mimicked by recurrent ischemic events in the early postangioplasty period. This group reported that 23% of patients developed recurrent ischemic events that were frequently silent or had a long silent period preceding the onset of pain. We selected only those patients who had shown ischemic ST changes

after PTCA, but found only 2 with recurrent ischemia (4% incidence). In both, ischemia produced ST elevation, which preceded chest pain and was useful in deciding on appropriate management. The relatively low incidence of recurrent ischemic events in our patients may relate to routine use of aspirin, which was not the case in the patients studied by Krucoff.¹

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Value of Thallium-201 Reinjection After Delayed SPECT Imaging for Predicting Reversible Ischemia After Coronary Artery Bypass Grafting

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The reinjection of a small dose (40 MBq) of thallium-201 after stress and delayed imaging often shows new redistribution in the regions with persistent defect. To assess whether these segments may represent reversible ischemia, reinjection thallium-201 single-photon emission computed tomography (SPECT) was performed after stress and 3-hour delayed imaging in 24 patients before coronary artery bypass grafting (CABG). The left ventricular myocardium was divided into 5 myocardial segments and regional wall motion was scored on a scale from 0 (normal) to 4 (dyskinesia). Thallium-201 findings were compared with improvement in regional perfusion and wall motion 1 to 2 months after CABG. The reinjection imaging identified new redistribution in 15 of 32 persistent defects (47%) on the 3-hour delayed images. In the study of stress and delayed SPECT imaging, the improvement in perfusion was observed in 34 of 43 segments (79%) exhibiting redistribution and 15 of 32 (47%) segments without redistribution ($p < 0.01$). The reinjection SPECT identified new redistribution in 12 of the 15 improved segments that were not detected on the delayed images. Similarly, the improvement in wall motion was observed in 23 of 31 segments (74%) exhibiting redistribution and 14 of 30 segments (47%) without redistribution on the delayed images ($p < 0.05$). The reinjection identified new redistribution in 10 of the 14 improved segments that were undetected on the delayed images. The predictive values for improvement in perfusion and wall motion by the reinjection imaging were significantly higher (92 and 89%) than those by the delayed imaging (69 and 62%, respectively, $p < 0.05$ each). Thus, reinjection thallium-201 SPECT should be performed for identifying reversible ischemic segments that are likely to improve in regional function after CABG when the routine stress and delayed imaging showed no redistribution.

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Stress thallium-201 perfusion imaging has been widely used for the detection of coronary artery disease and the identification of reversible ischemia.¹⁻⁷ Initial perfusion defects with redistribution on the delayed images are considered to represent ischemic but viable myocardium,³ while persistent defects without redistribution are usually considered as myocardial scar.⁸⁻¹¹ However, recent reports described the limitation of this criteria, because persistent defects often contain reversible ischemia after revascularization.¹²⁻¹⁶ Some investigators reported the value of late (24 to 72 hours) delayed imaging that improved the detection of viable myocardium.¹⁷⁻¹⁹ However, it is often difficult to assess redistribution due to low count density of thallium-201. Recently, Rocco et al²⁰ described the reinjection of a small dose of thallium-201 after delayed imaging that often shows new fill-in in the regions exhibiting persistent defect on the delayed images. However, whether such segments really represent reversible ischemia after revascularization remains unknown. Therefore, this study assesses how accurately the preoperative reinjection thallium-201 imaging predicts the improvement in perfusion and wall motion after coronary artery bypass grafting (CABG).

METHODS

Patient population: This study population was made up of 24 patients (18 men and 6 women) referred for CABG who underwent reinjection thallium-201 imaging after stress and delayed imaging before CABG. The age range was 50 to 75 years with a mean of 61.7. Fourteen patients had a history of myocardial infarction.

Stress thallium-201 imaging: Each patient underwent stress thallium-201 imaging 1 week before CABG and repeated it 4 to 8 weeks after CABG.

The exercise level started at 25 watts and increased an additional 25 watts every 3 minutes using an upright bicycle ergometer. Each patient exercised to the onset of angina pain, dyspnea, ST-segment depression (>0.2 mV), a decrease in blood pressure or until 85% of the age-predicted maximal heart rate. One minute before completion of exercise, approximately 100 MBq (2.7 mCi) of thallium-201 chloride was administered intravenously. Postexercise perfusion imaging was performed within 10 minutes after the tracer injection. After 3-hour delayed imaging, additional 40 MBq (1.1 mCi) of thallium-201 chloride was administered and the reinjection imaging was obtained 10 minutes later. In each thallium-201 study, single-photon emission computed tomography (SPECT) was applied, collecting 32 views

over 180° for 30 seconds each, as described previously.²¹⁻²³ After CABG, the post-stress and 3-hour delayed imaging was repeated with the similar exercise load.

A series of contiguous transverse slices of the left ventricular myocardium were reconstructed by filtered back projection method using a Ramp-Hanning filter with a cutoff frequency of 0.5 cycle/pixel and Y filter. No attenuation correction was used. These images were further processed to obtain the short-axis and long-axis sections perpendicular to the cardiac axes.²¹⁻²³

Wall motion analysis: Each patient underwent multigated radionuclide ventriculography in the anterior and left anterior oblique projections after intravenous injection of 740 MBq (20 mCi) of technetium-99m-labeled red blood cells before and after CABG. The left ventricle was divided into anterior, apical, inferior, septal and lateral segments. Wall motion was visually assessed by 2 experienced observers and graded on a scale of 0 to 4 (normal, mild hypokinesia, severe hypokinesia, akinesia or dyskinesia).²⁴

When the wall motion score decreased by ≥ 1 after the surgery, the segments were considered as improved wall motion postoperatively. The wall motion in septal segment was excluded in this analysis because paradoxical motion is occasionally observed postoperatively.^{24,25}

Interpretation of thallium-201 imaging: For visual interpretation, a series of short-axis, vertical long-axis, horizontal long-axis and transverse tomograms were displayed on transparent film with the intensity of each image normalized to the maximal pixel value on the image. Separate films were obtained displaying 16 slices of the stress, delayed and reinjection images.

The left ventricular myocardium was divided into 5 segments corresponding to those of regional wall motion analysis. All pre- and post-CABG thallium-201 images were scored separately by the consensus of 2 experienced observers using a 5-point grading system (0 = normal, 1 = equivocal, 2 = mild, 3 = moderate and 4 = severe decrease of thallium-201 uptake) without knowledge of the clinical history, electrocardiogram or angiographic results. A stress perfusion defect was considered present when a myocardial segment had an initial stress score >1 . Stress perfusion defects with a score zero on the delayed images were defined as complete redistribution. Stress perfusion defects with a decrease in score by ≥ 1 but not returned to zero were defined as incomplete redistribution. On the contrary, the defects with a same score on the delayed images were defined as persistent defects. The persistent defects were further categorized according to their score pattern on the reinjection images; those with a decrease in score on the reinjection images were defined as new redistribution after reinjection and those with the same score were defined as persistent defect after reinjection.

When the thallium-201 score on the delayed images decreased by ≥ 1 after CABG, the segments with perfusion defect were considered as an improvement in perfusion after CABG.

Coronary artery bypass grafting: All patients underwent grafting of the saphenous vein or internal mammary artery. One patient with 2-vessel disease received 1 bypass graft, 8 patients with 2-vessel disease

TABLE I Comparison of Thallium-201 Redistribution Obtained by 3-Hour Delayed Imaging and Reinjection Imaging

Delayed Imaging	Reinjection Imaging			Total
	Complete RD	Incomplete RD	PD	
Complete RD	2	0	0	2
Incomplete RD	10	31	0	41
PD	0	15	17	32
Total	12	46	17	75

RD = redistribution; PD = persistent defect.

TABLE II Relation of Preoperative Thallium-201 Imaging with Improvement in Regional Perfusion After Surgery

Thallium-201 Findings		Postoperative Perfusion		Total
Delayed	Reinjection	Improved	Not Improved	
RD	RD	34	9	43
PD	New RD	12	3	15
PD	No RD	3	14	17
Total		49	26	75

* $p < 0.01$.

had 2 grafts, 9 patients with 3-vessel disease had 2 grafts, 4 patients with 3-vessel disease had 3 grafts and 2 patients with the left main trunk lesion had 2 grafts. Of 51 total bypass grafts, 48 (94%) were patent on the arteriography performed 1 month after CABG. Patients with evidence of a perioperative myocardial infarction were excluded from this study.

Statistical analysis: Comparisons of proportions were performed by way of chi-square analysis or Fisher's exact test. Probability values <0.05 were considered significant.

RESULTS

Preoperative thallium-201 findings: Preoperative stress and delayed thallium-201 imaging detected perfusion abnormality in 75 segments, including 2 segments with complete redistribution, 41 segments with incomplete redistribution and 32 segments with persistent defect (Table I). The stress and reinjection thallium-201 imaging showed 12 segments with complete redistribution, 46 segments with incomplete redistribution and 17 segments with persistent defect. Of 75 segments with abnormal perfusion preoperatively, concordant findings were observed in 56 segments (67%) between the delayed and reinjection imaging. However, the reinjection imaging exhibited incomplete redistribution in 15 of 32 persistent defects and complete redistribution in 10 of 41 segments with incomplete redistribution on the delayed images (Table I). Interobserver variability was 5.8% on the delayed images and 5.0% on reinjection images.

Preoperative thallium-201 findings versus improvement in perfusion: Of 75 hypoperfused segments preoperatively, 49 segments improved in perfusion and the remaining 26 segments did not improve after CABG (Table II). Of 43 segments with redistribution on the delayed images, 34 improved in perfusion but 15 of the 32 with persistent defect also improved after CABG (p

<0.01 , Table II). Thus, improvement in perfusion was accurately predicted in 69% (34 of 49), while no improvement in perfusion was correctly predicted in 65% (17 of 26) by the stress and delayed imaging.

The reinjection imaging identified new redistribution in 15 of the 32 segments (47%) with persistent defect on the delayed images. Twelve of them showed improvement in perfusion (Figures 1 and 2), while only 3 segments exhibiting no redistribution after reinjection improved in perfusion ($p < 0.01$, Table II). Thus, the reinjection imaging accurately identified 80% of the improved segments showing persistent defect on the de-

layed images. The predictive value for improvement in perfusion by the reinjection imaging was 92% (46 of 49), which was significantly higher than the value obtained by the delayed imaging (69%, $p < 0.05$), although the predictive values for no improvement in perfusion were similar between the 2 studies (54 and 65%, respectively, Table III).

Preoperative thallium-201 findings versus improvement in wall motion: Of 61 hypoperfused segments studied for wall motion analysis, 16 segments showed normal motion and 45 segments showed abnormal wall motion, preoperatively (Table III). After CABG, 37

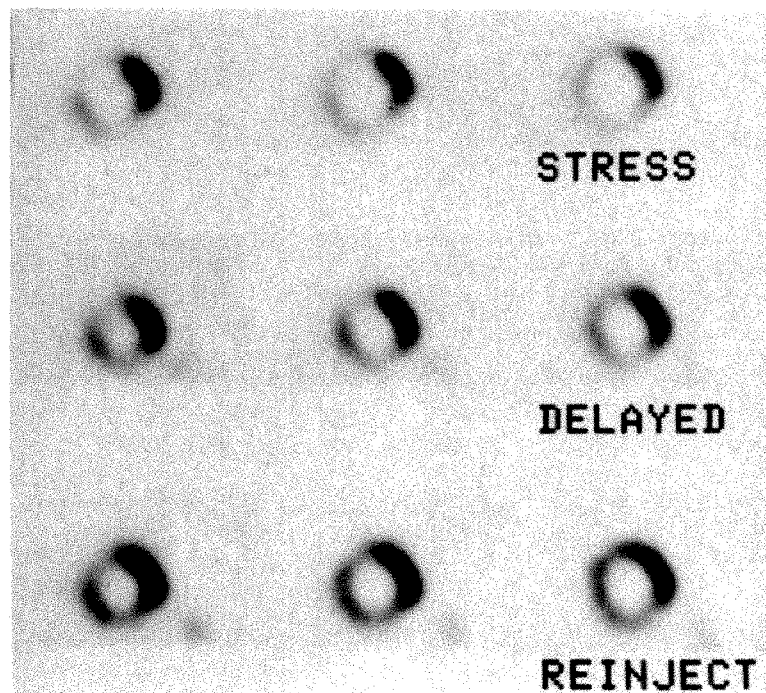


FIGURE 1. Three representative short-axis slices of stress (*top*), delayed (*middle*) and reinjection (*bottom*) images of a 64-year-old patient with anterior and inferior wall myocardial infarction. A large perfusion defect in anterior, septal and inferior segments is observed on the stress images. The delayed images show no definite redistribution in anterior and inferior segments except slight redistribution in septal segment. The reinjection images, however, show definite fill-in (redistribution) in anterior, inferior and septal segments.

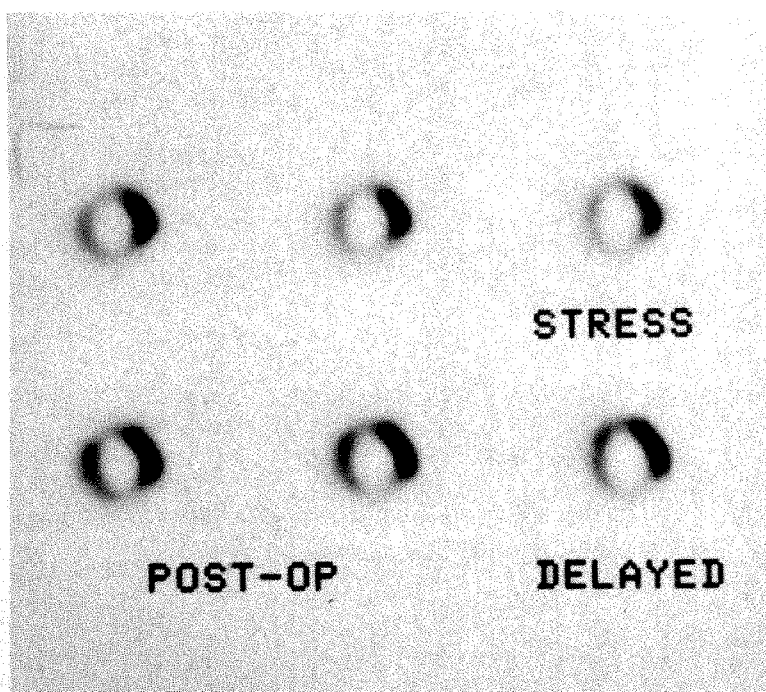


FIGURE 2. Short-axis slices of stress (*top*) and delayed (*bottom*) images of the same patient after coronary bypass surgery. Note improvement in perfusion in anterior and septal segments.

segments exhibited normal or improved wall motion, but 24 segments did not show improvement in wall motion. Of 31 segments showing redistribution on the delayed images before CABG, 23 had normal or improved wall motion and the remaining 8 did not improve in wall motion after CABG ($p < 0.05$). However, 14 of the 30 segments without redistribution on the delayed images also had normal or improved wall motion. Thus, the stress and delayed imaging accurately predicted improvement in wall motion in 62% (23 of 37) and no improvement in wall motion in 67% (16 of 24).

The reinjection imaging identified new redistribution in 14 of the 30 segments with persistent defect (47%) on the delayed images (Table III). Ten of them showed improved wall motion (Figures 1 and 3), while only 4 segments without new redistribution improved in wall motion. Thus, the predictive value for improvement in wall motion by the reinjection imaging was 89% (33 of 37), which was significantly higher than that by the delayed imaging (62%, $p < 0.05$), although the predictive values for no improvement in wall motion were similar between them (50 and 67%, respectively).

TABLE III Relation of Preoperative Thallium-201 Imaging with Improvement in Regional Wall Motion After Surgery

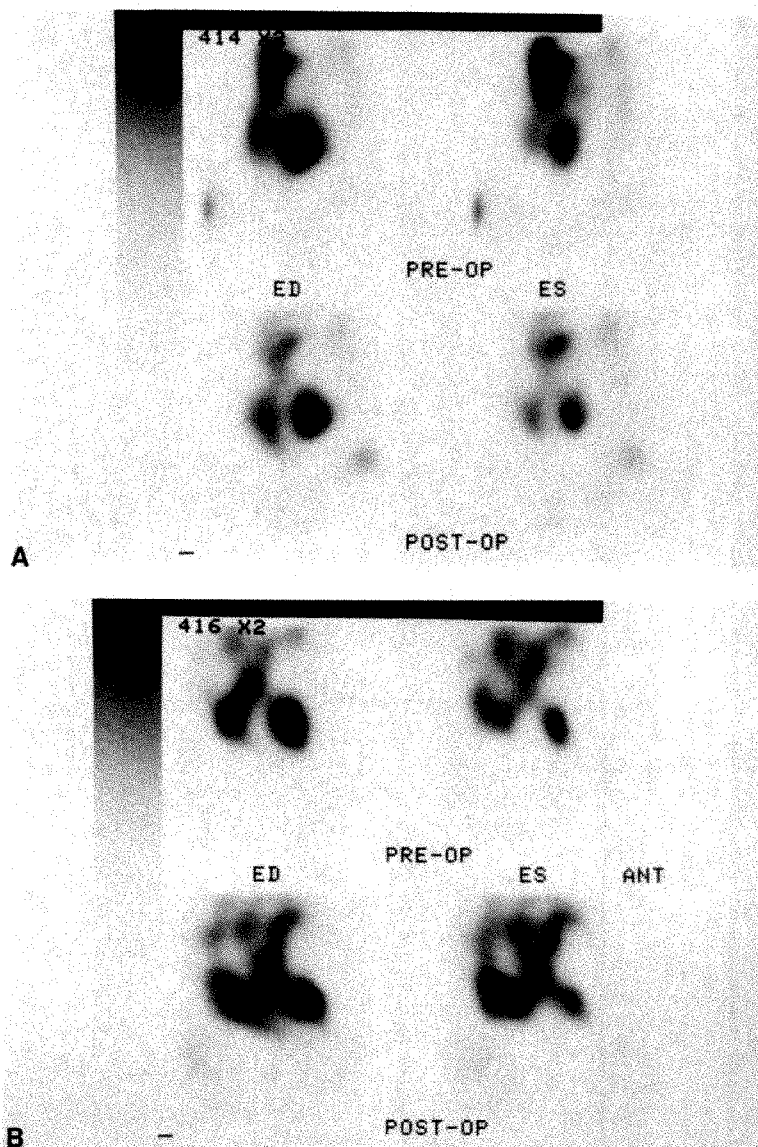
Thallium-201 Findings		Postoperative Wall Motion		
		Normal or Improved	Not Improved	Total
Delayed	Reinjection			
RD	RD	23	8	31
PD	New RD	10	4	14
PD	No RD	4	12	16
Total		37	24	61

* $p < 0.01$.

DISCUSSION

Identification of ischemia by delayed imaging: In our study, 79 and 74% of the segments showing redistribution on 3-hour delayed images improved in regional perfusion and wall motion after CABG, respectively. These values were consistent with previous reports,¹²⁻¹⁵ indicating that the segments showing redistribution represent ischemic but viable myocardium, as evidenced by the improvement after revascularization.¹²⁻¹³

FIGURE 3. Preoperative (PRE-OP, top) and postoperative (POST-OP, bottom) radionuclide ventriculography in left anterior oblique projection (A) and anterior projection (B) of the same patient. Preoperative study shows akinesis in apical, septal and anterior segments and hypokinesis in inferior segment with moderate left ventricular dilatation. The postoperative study shows improvement in asynergy in apical and anterior segments with improvement in left ventricular dilatation.



On the other hand, 47% of the persistent defects without redistribution on the delayed images also improved in perfusion and wall motion after CABG, respectively. These values were consistent with reports by other investigators¹²⁻¹³ describing improvement in regional function in 45 to 75% of myocardial segments with persistent defect. In addition, in the study of positron emission tomography, Brunken et al¹⁴ and ourselves¹⁵ showed that metabolically viable myocardium was occasionally observed in persistent defects. These observations suggest that the stress and delayed thallium-201 imaging may underestimate the presence of ischemic but viable myocardium because of the limitation of the persistent defects on 3-hour delayed images as a marker of nonviable myocardium.

Value of reinjection thallium-201 imaging: The reinjection thallium-201 imaging identified new redistribution in 47% of those exhibiting persistent defect on the delayed images and 71 to 80% of these segments showed improvement in regional perfusion and wall motion after CABG, yielding higher predictive values for such improvement by the reinjection imaging. The preliminary studies showed that the wall motion in such segments tended to be more preserved than those without redistribution after reinjection.^{20,26} These data indicate that the reinjection thallium-201 imaging may accurately show very mild redistribution that indicates reversible ischemia but were not identified by the delayed imaging. In addition, the recent preliminary studies indicate that the segments showing new redistribution have persistent metabolic activity on positron tomography.^{27,28}

Our previous data indicated the importance of segments showing very mild or "minimal" redistribution which usually contained metabolically viable myocardium.²⁹ However, the presence of such trivial redistribution may not be confident by the routine thallium-201 imaging. In this respect, the reinjection thallium-201 imaging may help clarify the presence or absence of such redistribution in the hypoperfused areas using higher quality images with more count density than the 3-hour or late delayed images. The entire study may be completed within 4 hours on the same day, which is feasible to perform, particularly in outpatients. The total administration dose (140 MBq) seems to be acceptable.

Mechanisms of new redistribution after reinjection: Thallium-201 distribution after reinjection may closely represent resting perfusion and delayed distribution after exercise. Blood et al³ compared the delayed images and resting images to describe the tendency of larger perfusion defects on the former. Our previous data also indicated that 2 separate injections of the perfusion agent (n = 13, ammonia) during stress and resting identified reversible ischemia more often than the single injection of thallium-201.^{16,30} Thus, it may take longer than 3 to 4 hours to reach the equilibrium of thallium-201 in the potassium pool in the viable tissue after exercise. In this respect, the reinjection or late redistribution imaging will help reach this equilibrium to show new redistribution more often.^{18,19}

In addition, redistribution also depends on plasma concentration of thallium-201 and low plasma concentration may often prevent redistribution in the ischemic areas without evidence of myocardial infarction.³¹⁻³³ The reinjection of thallium-201 increases plasma concentration of the tracer, which may facilitate redistribution in the ischemic myocardium.

Clinical implications: Our results suggest that small dose of thallium-201 reinjection after delayed imaging identified new redistribution in 70 to 80% of the reversible ischemic segments where redistribution was undetected by the routine stress and delayed imaging. Thus, the reinjection imaging appears to be a useful noninvasive means for accurate prediction of reversible ischemic myocardium, which is likely to improve in regional function after CABG, particularly when the routine thallium-201 imaging shows persistent defects.

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Preservation of Left Ventricular Performance with Reduced Ischemic Dysfunction by Intravenous Nisoldipine

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The effect of intravenous nisoldipine on cardiac performance was examined during pacing-induced ischemia in 14 patients with coronary artery disease. The relative contributions of afterload reduction or prevention of myocardial ischemia were assessed using load-independent global (peak-systolic pressure/end-systolic volume) and regional (peak-systolic pressure/end-systolic radial length) "contractile" indexes. Nisoldipine decreased aortic pressure (predrug, 109 ± 14 vs postdrug, 88 ± 13 mm Hg, $p < 0.01$) and prevented elevation of left ventricular end-diastolic pressure during rapid atrial pacing (predrug, 7.9 ± 5.7 vs postdrug, -0.5 ± 4.9 mm Hg, $p < 0.001$). Resting cardiac index (predrug, 3.3 ± 0.6 vs postdrug, 4.2 ± 0.7 liters/min/m², $p < 0.05$), and left ventricular ejection fraction (predrug, 68.1 ± 9.0 vs postdrug, $74.2 \pm 9.4\%$, $p < 0.05$) increased after nisoldipine, which also prevented the deterioration in left ventricular ejection fraction (predrug, -8.1 ± 7.9 vs postdrug, $-1.0 \pm 3.7\%$, $p < 0.05$) and fractional radial shortening (predrug, -8.7 ± 13.1 vs postdrug, $3.7 \pm 16.4\%$, $p < 0.01$) during rapid atrial pacing. Under these conditions, nisoldipine preserved myocardial function, as determined by global peak-systolic pressure/end-systolic volume (predrug, -0.82 ± 0.39 vs postdrug, 0.17 ± 1.54 mm Hg/ml, $p < 0.05$) and regional (peak-systolic pressure/end-systolic radial length, predrug, -23.8 ± 36.1 vs postdrug, 12.7 ± 36.3 mm Hg/cm, $p < 0.01$) "contractile" indexes. Intravenous nisoldipine maintains ventricular performance during rapid atrial pacing via a combination of systemic vasodilation and amelioration of ischemic myocardial dysfunction.

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Nisoldipine is a second-generation dihydropyridine derivative with proven efficacy in controlling angina pectoris.^{1,2} This ester-substituted analog of nifedipine has high vascular selectivity,³ while exhibiting minimal negative inotropic properties.⁴ Nisoldipine is noted to decrease systemic vascular resistance, thus increasing resting left ventricular stroke volume, ejection fraction and systemic cardiac output, yet little information is available under ischemic conditions in man. This study evaluates the effect of intravenous nisoldipine on resting cardiac performance and the preservation of left ventricular ejection parameters during pacing-induced angina pectoris.^{5,6} Since cardiac performance is a function of both ventricular afterload (systolic wall stress) and intrinsic myocardial contractility, we calculated load-independent global (peak-systolic pressure/end-systolic volume) and regional (peak-systolic pressure/end-systolic radial length) "contractile" indexes to assess the severity of ischemic dysfunction.⁷⁻⁹

METHODS

Subject population: We studied 14 patients (13 men, 1 woman) with a mean age of 55 years (range 41 to 72), presenting for diagnostic coronary arteriography. Each participant showed mild to moderate (Canadian Cardiovascular Study class I to III/IV) stable exertional angina pectoris, with objective evidence of myocardial ischemia via standard exercise testing or thallium scintigraphy. Before the study, all patients were receiving some form of antianginal therapy (nitrates [4], β blockers [11], calcium antagonists [11]), while 7 of 14 (50%) had remote myocardial infarctions. The extent/severity of coronary stenoses varied (stenotic diameter <1.0 mm, "normal" [1], 1-vessel disease [2], 2-vessel disease [6] and 3-vessel disease [5]); as did ventricular function (left ventricular ejection fraction $>60\%$ [4], 40 to 59% [6], $<40\%$ [4]). Exclusion criteria consisted of unstable angina, recent myocardial infarction (<3 months), congestive heart failure or severe left ventricular dysfunction (ejection fraction $<30\%$), significant arrhythmias, peripheral vascular disease, renal insufficiency (creatinine >150 mmol/liter), dihydropyridine intolerance or absence of informed consent. The study protocol was approved by the Human Subjects Review Committee (Toronto General Hospital) and the Health Protection Branch, Department of Health and Welfare, Ottawa, Ontario, Canada.

Procedures: HEART CATHETERIZATION/ANGIOGRAPHY: All subjects were studied in a postabsorptive state, with antianginal medications withheld for 24 hours. Pre-medication consisted of diazepam (10 mg) while no par-

participant received atropine sulfate or sublingual nitroglycerin within 2 hours of the study. Instrumentation was performed via the femoral route under local anesthesia (2% lidocaine). A Cordis 8Fr "pigtail" catheter was positioned in the left ventricle for end-diastolic pressure measurement and standardized contrast ventriculography. Left ventricular end-diastolic pressure was consistently recorded by "instantaneously" lowering the pacing rate to baseline (80 beats/min) values. Quantitative ventriculography was performed in a 30-degree right anterior oblique projection at 30 frames per second, using 45 ml (15 ml/s \times 3 s) of a nonionic contrast media (iohexol 350). A 6Fr Kifa endhole catheter was advanced to the ascending aorta for assessment of systemic pressure. A 6Fr bipolar pacing catheter was placed at the right atrial-superior venacaval junction to allow rapid atrial pacing. A 7Fr balloon flotation (Swan-Ganz) thermodilution catheter was positioned in

the pulmonary artery for pressure measurement and determination of cardiac output (in triplicate).

PROTOCOL: Baseline pacing was initiated at 80 beats/min; a value exceeding the intrinsic sinus rate by ≥ 10 beats/min, with all measurements recorded (baseline₁). The heart rate was accelerated (10 beats/min, every 3 minutes) until mild to moderate (subjective scale 3 to 5/10) "typical" angina was experienced. While chest discomfort was reported, all measurements were repeated (pacing₁). Atrial pacing was discontinued and a hemodynamic stabilization period (10 minutes) was observed. While rigorous light protection was maintained, intravenous nisoldipine was initially given as a bolus (30 seconds) injection (1.0 μ g/kg), followed by a continuous infusion (0.5 μ g/kg/min, \times 5 min), for a total dose equal to 3.5 μ g/kg. Baseline atrial pacing was recommenced (80 beats/min), with all measurements repeated (baseline₂). The same maximal heart rate was at-

FIGURE 1. Cardiac index (cardiac output/body surface area) during experimental protocol (individual values and group means). NS = not significant.

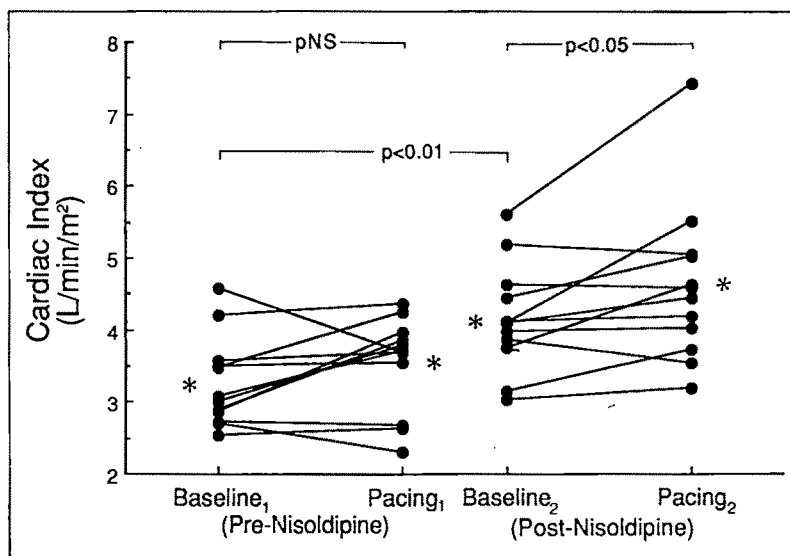
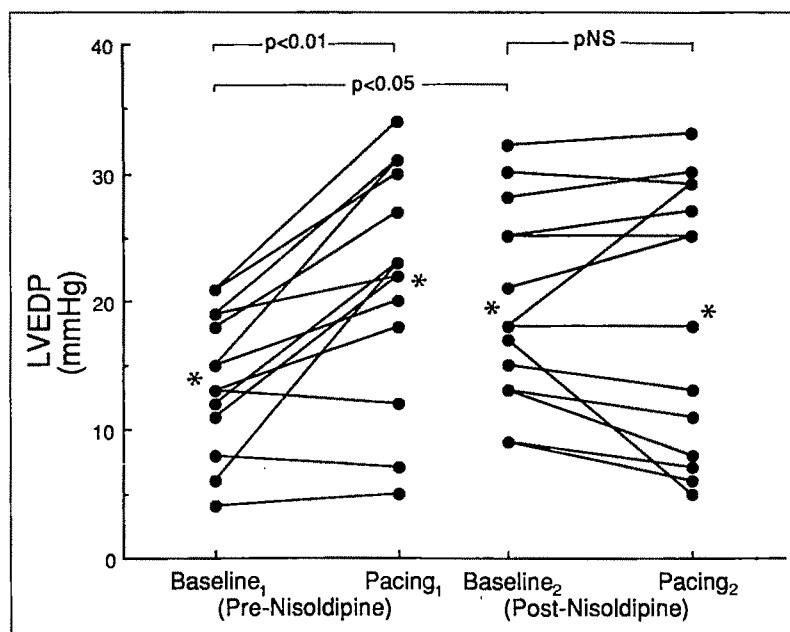


FIGURE 2. Left ventricular end-diastolic pressure during experimental protocol (individual values and group means). LVEDP = left ventricular end-diastolic pressure; NS = not significant.



tained after an identical pacing protocol, with all measurements repeated (pacing₂). After protocol completion, multi-angulated (cranial/caudal) coronary arteriography was performed in a routine fashion.

Analysis: QUANTITATIVE VENTRICULOGRAPHY: Ventriculograms were analyzed in a consistent fashion by a single observer. Calibrated diastolic and systolic frames were identified from optimally opacified cardiac cycles, while specifically avoiding ventricular ectopic beats. A Vanguard-television camera system was used to project the images directly onto an image processing computer (Kontron Cardio-200). Absolute ventricular volumes were calculated (modified Simpson's rule) using manually defined endocardial borders. Regional wall motion analysis (48 radians) used a floating "center of contraction," with the calculation of fractional radial shortening and absolute end-systolic radial length. Myocardial "contractility" was assessed using global (peak-systolic pressure/end-systolic volume) and regional (peak-systolic pressure/end-systolic radial length) indexes.⁷⁻⁹

Statistics: Individual values with means and standard deviations are presented. Clinically, relevant comparisons were performed between "baseline" values ($B_2 - B_1$) and during initial rapid atrial pacing ($P_1 - B_1$). Nisoldipine's effect on ischemic ventricular function was measured by comparing the differences during an identical pacing protocol before and after drug administration [$(P_1 - B_1) - (P_2 - B_2)$]. All comparisons used analysis of variance (ANOVA), while statistical significance was defined as a p value <0.05.

RESULTS

Clinical: The protocol was well tolerated, although mild generalized "flushing" was noted by 3 subjects. Atrial fibrillation developed in 1 subject, with resultant moderate angina pectoris. Otherwise, precordial discomfort was highly predictable during atrial pacing. Mild to moderate precordial discomfort was initially elicited in all subjects, although only 6 of 14 (43%) re-experienced chest pain after intravenous nisoldipine.

Hemodynamics: During rapid atrial pacing, mean aortic pressure increased (pre-pacing, 109 ± 14 vs post-pacing, 116 ± 17 mm Hg, $p < 0.05$), predominantly secondary to an increase in diastolic pressure (pre-pacing, 89 ± 9 vs postpacing, 100 ± 14 mm Hg, $p < 0.05$). Intravenous nisoldipine produced a moderate decrease in mean arterial pressure (predrug, 109 ± 14 vs postdrug, 88 ± 13 mm Hg, $p < 0.01$), with a decrease in double product (maximum heart rate \times systolic blood pressure) during atrial pacing (predrug, $19,188 \pm 240$ vs postdrug, $16,236 \pm 152$, $p < 0.01$). Pulmonary artery pressure was unchanged during angina pectoris (pre-pacing, 17 ± 3 vs postpacing, 19 ± 5 mm Hg, difference not significant) but was slightly increased after nisoldipine (predrug, 17 ± 3 vs postdrug, 22 ± 6 mm Hg, $p < 0.01$). Figure 1 shows changes in cardiac index during atrial pacing, before and after the nisoldipine infusion. Atrial pacing failed to alter cardiac index (pre-pacing, 3.3 ± 0.6 vs postpacing, 3.5 ± 0.6 liters/min/m², difference not significant), although cardiac index was substantially increased after nisoldipine (predrug, $3.3 \pm$

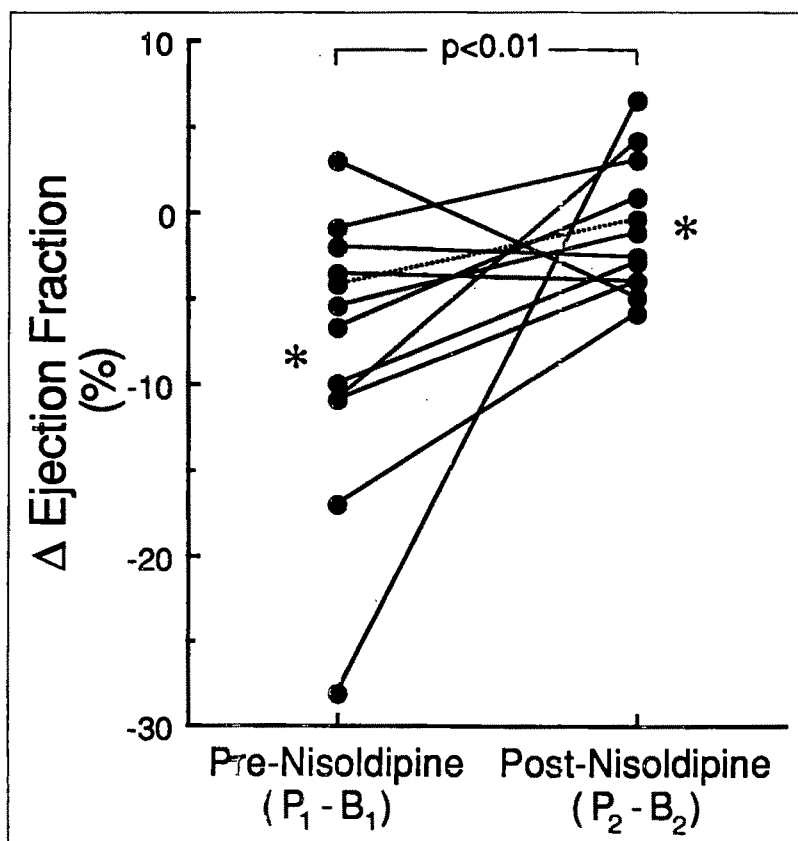


FIGURE 3. Changes in left ventricular ejection fraction during rapid atrial pacing, before and after nisoldipine (individual values and group means).

0.6 vs postdrug, 4.2 ± 0.7 liters/min/m², $p < 0.01$). These changes can be attributed to a decrease in systemic vascular resistance (predrug, $1,464 \pm 431$ vs postdrug, 906 ± 205 dynes s cm⁻⁵, $p < 0.01$), with no difference in pulmonary vascular resistance (predrug, 215 ± 71 vs postdrug, 220 ± 96 dynes s cm⁻⁵, difference not significant). Figure 2 shows left ventricular end-diastolic pressure during the protocol. Left ventricular end-diastolic pressure was increased by rapid atrial pacing (prepacing, 13.9 ± 5.2 vs postpacing, 21.8 ± 8.6 mm Hg, $p < 0.01$), although these changes were completely abolished by nisoldipine (prepacing, 19.5 ± 7.3 vs postpacing, 19.0 ± 9.9 mm Hg, difference not significant).

Ventricular performance: Calculated left ventricular end-diastolic volume failed to change significantly during rapid atrial pacing (prepacing, 125 ± 32 vs postpacing, 126 ± 38 ml, difference not significant), with a trend to increased diastolic volumes after nisoldipine (predrug, 125 ± 32 vs postdrug, 140 ± 41 ml, $p < 0.1$). During rapid atrial pacing, left ventricular end-systolic volume increased (prepacing, 40 ± 16 vs postpacing, 50 ± 26 ml, $p < 0.05$), although these changes were largely prevented by nisoldipine (predrug, 12.7 ± 13.1 vs postdrug, 3.2 ± 11.5 ml, $p < 0.05$). Nisoldipine significantly improved resting left ventricular ejection fraction (predrug, 68 ± 9 vs postdrug, $74 \pm 9\%$, $p < 0.05$). Figure 3 shows changes in left ventricular ejection fraction during rapid atrial pacing, before and after nisoldipine. This medication markedly blunted the deterioration in cardiac index (predrug, -8.1 ± 7.9 vs postdrug, $-1.0 \pm 3.7\%$, $p < 0.01$) caused by atrial pacing. Figure 4 shows changes in regional wall motion during the experimen-

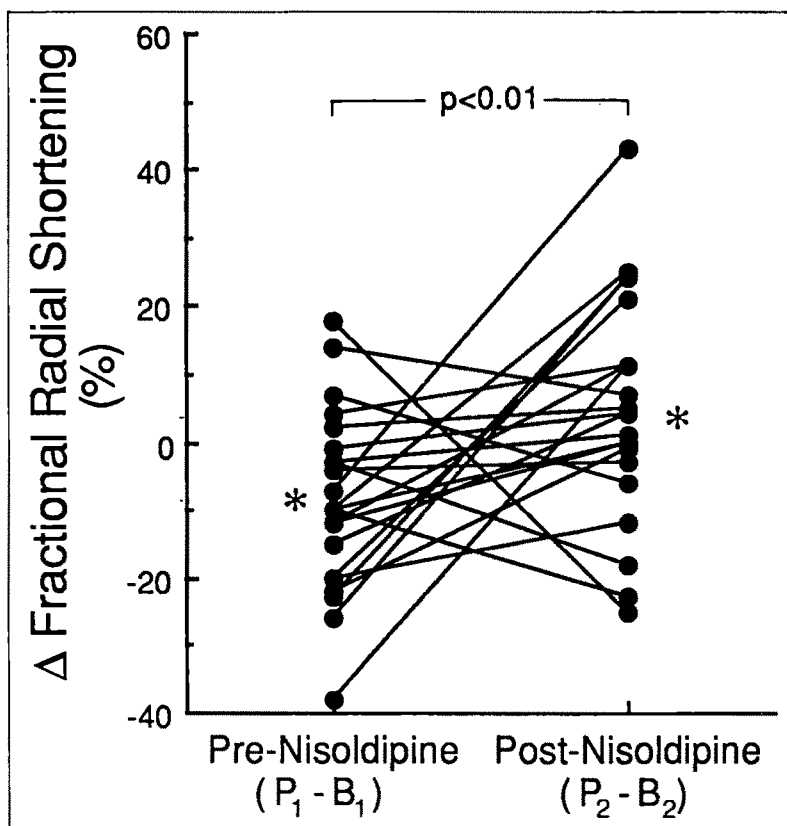
tal protocol. Fractional radial shortening decreased during rapid pacing, while this deterioration was prevented by nisoldipine (predrug, -8.7 ± 13.1 vs postdrug, $3.7 \pm 16.4\%$, $p < 0.01$). Absolute end-systolic radial length increased during rapid atrial pacing (inferior, 1.50 ± 0.29 to 1.54 ± 0.37 cm, difference not significant, and anterior, 0.90 ± 0.35 to 1.01 ± 0.42 cm, $p < 0.05$), while nisoldipine prevented these changes (inferior, 1.44 ± 0.34 to 1.35 ± 0.31 cm, difference not significant, and anterior, 0.90 ± 0.54 to 0.80 ± 0.32 cm, $p < 0.05$).

Myocardial contractility: Figure 5 shows changes in the global left ventricular "contractile" index, as the peak-systolic pressure/end-systolic volume, during rapid atrial pacing. Appreciable deterioration in myocardial contractility was noted, but was completely eliminated by nisoldipine (predrug, -0.82 ± 0.39 vs postdrug, 0.17 ± 1.54 mm Hg/ml, $p < 0.05$). Figure 6 shows regional "contractile" function, as the ratio of peak-systolic pressure/end-systolic radial length before and after intravenous nisoldipine. Nisoldipine prevented the previously observed decrease in segmental ventricular function (predrug, -23.8 ± 36.1 vs postdrug, 12.7 ± 36.3 mm Hg/cm, $p < 0.01$) during atrial pacing.

DISCUSSION

Resting hemodynamics: Nisoldipine's effects on systemic hemodynamics and resting left ventricular function are relatively well characterized. Duncker¹⁰ described tachycardia (+70%), decreased aortic pressure (-21%) with increased cardiac output (+67%) in pigs after oral nisoldipine (10 mg). Nienaber¹¹ compared the acute hemodynamic response to nisoldipine and nifedi-

FIGURE 4. Changes in fractional radial shortening during rapid atrial pacing, before and after nisoldipine (individual values and group means).



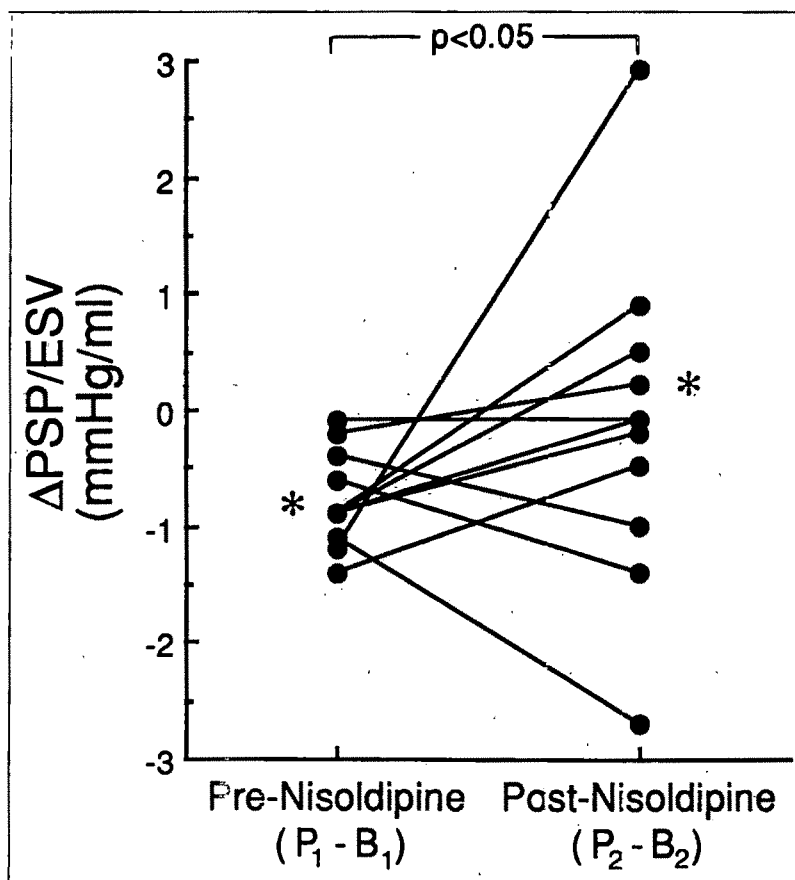


FIGURE 5. Changes in global ventricular "contractile index," peak-systolic pressure/end-systolic volume ($\Delta\text{PSP/ESV}$), during rapid atrial pacing before and after nisoldipine (individual values and group means).

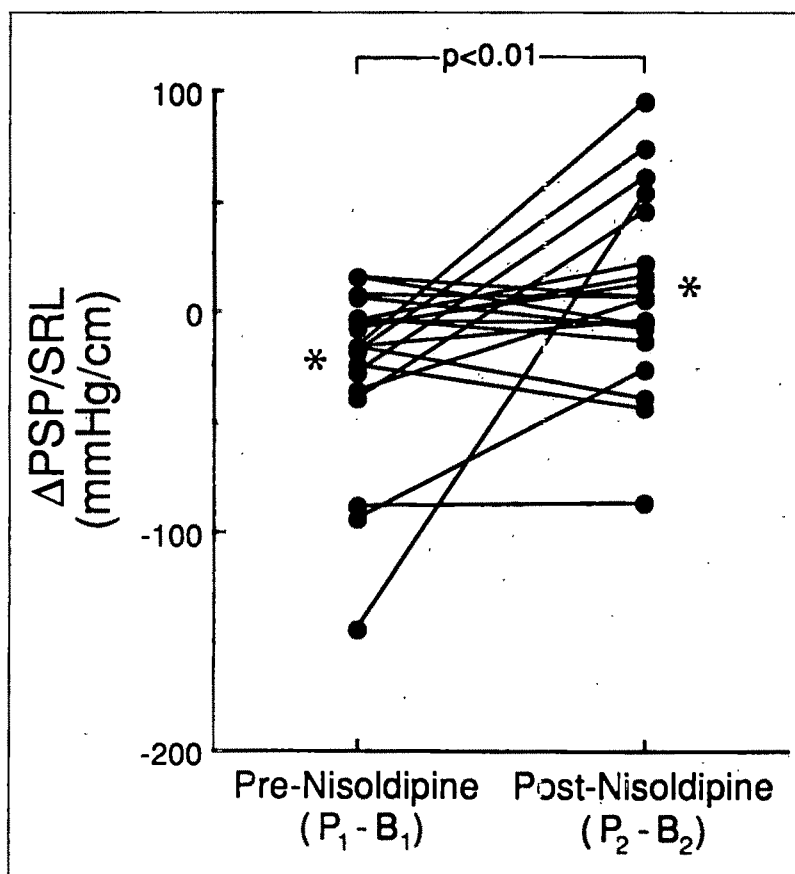


FIGURE 6. Changes in regional ventricular "contractile index," peak-systolic pressure/end-systolic radial length ($\Delta\text{PSP/SRL}$), during rapid atrial pacing, before and after nisoldipine (individual values and group means).

pine in a crossover trial after myocardial infarction. They observed a significant increase in left ventricular stroke volume, ejection fraction and cardiac index, while noting a decrease in pulmonary capillary wedge pressure. These findings were independently confirmed by Soward¹² and are in accordance with this investigation. In addition to the effect of nisoldipine on systolic function (ejection fraction, peak ejection rate), Otto¹³ observed improved diastolic ventricular function, as determined by peak-filling rate ($+0.52$ end-diastolic volume/s) in patients with coronary artery disease.

Exercise performance: Before nisoldipine infusion, a marked increase in left ventricular end-diastolic pressure was observed during rapid atrial pacing and, in the context of obstructive coronary disease, is compatible with ischemic ventricular dysfunction. Nisoldipine largely prevented these changes, while maintaining global and regional left ventricular systolic function, as determined by angiographic left ventricular ejection fraction, stroke volume and fractional radial shortening. Crean¹⁴ studied oral nisoldipine's (20 mg) effect during standard exercise testing in patients with coronary artery disease. These investigators observed a significant decrease in systemic pressure, increased exercise duration, and a prolongation in time to ischemia (electrocardiographic criteria). Dymond et al.⁵ evaluated the influence of oral nisoldipine (10 mg) on exercise ventricular function by radionuclide angiography. An increased exercise duration was noted, with the elimination of exercise-induced regional wall motion abnormalities at identical workloads. Using a nonimaging nuclear probe, Silke¹⁶ confirmed these results after intravenous nisoldipine and concluded that nisoldipine improved both resting and exercise cardiac performance.

Potential mechanisms: Based on sequential analysis of global and regional load-independent "contractile" indexes, the amelioration of myocardial ischemic dysfunction is partially responsible for the maintenance of cardiac performance during rapid atrial pacing. A number of potential mechanisms may be operational. Myocardial oxygen demand could be decreased by alterations in left ventricular systolic wall stress (afterload), or nisoldipine may exert a more potent negative inotropic influence under these conditions than previously described. Only limited information is available regarding changes in myocardial oxygen consumption after nisoldipine. Soward et al.¹⁷ failed to observe any significant change in myocardial oxygen consumption because decreased aortic pressure was precisely counter-balanced by an increase in heart rate. Rousseau¹⁸ confirmed these findings during cold pressor testing, but also noted improved regional aerobic metabolism, as determined by C^{14} -lactate extraction ratios. Alternatively, nisoldipine could eliminate myocardial ischemia by increasing coronary blood flow via vasodilation of distal resistance vessels. Serruys¹⁹ showed a substantial (21%) increase

in coronary blood flow after intravenous nisoldipine, while Duncker²⁰ suggested preferential distribution to the subepicardial layers. These observations were independently confirmed by Soward¹⁷ during rapid coronary sinus pacing and Rousseau¹⁸ after cold pressor testing.

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Usefulness of Semiquantitative Analysis of Dipyridamole-Thallium-201 Redistribution for Improving Risk Stratification Before Vascular Surgery

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Preoperative dipyridamole-thallium-201 scanning is sensitive in identifying patients prone to ischemic cardiac complications after vascular surgery, but most patients with redistribution do not have an event after surgery. Therefore, its positive predictive value is limited. To determine which patients with thallium redistribution are at highest risk, dipyridamole-thallium-201 images were interpreted semiquantitatively. Sixty-two consecutive patients with redistribution on preoperative dipyridamole-thallium-201 planar imaging studies were identified. Each thallium scan was then analyzed independently by 2 observers for the number of myocardial segments out of 15, the number of thallium views out of 3 and the number of coronary artery territories with redistribution. Seventeen patients (27%) had postoperative ischemic events, including unstable angina pectoris, ischemic pulmonary edema, myocardial infarction and cardiac death. Thallium predictors of ischemic operative complications included thallium redistribution ≥ 4 myocardial segments ($p = 0.03$), ≥ 2 of the 3 planar views ($p = 0.005$) and ≥ 2 coronary territories ($p = 0.007$). No patient with redistribution in only 1 view had an ischemic event (0 of 15). Thus, determining the extent of redistribution by dipyridamole-thallium-201 scanning improves risk stratification before vascular surgery. Patients with greater numbers of myocardial segments and greater numbers of coronary territories showing thallium-201 redistribution are at higher risk for ischemic cardiac complications. In contrast, when the extent of thallium redistribution is limited, there is a lower risk despite the presence of redistribution.

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Coronary artery disease is common in patients presenting for vascular surgery and is unsuspected in many because of the sedentary lifestyle enforced by arterial insufficiency. As a result, vascular surgery has been associated with a relatively high rate of ischemic cardiac complications.¹⁻⁶ Dipyridamole-thallium-201 imaging, a pharmacologic, nonexercise stress test, has been shown to be sensitive in assessing operative risk, but only a minority of patients with redistribution will have events.⁷⁻⁹ The clinical problem, then, is management of the patient with a positive preoperative scan.

One approach to this problem has been to add information based on clinical variables.^{10,11} In contrast, we hypothesized that risk stratification based on the extent of thallium-201 redistribution might be possible. We now report a simple semiquantitative approach to the interpretation of preoperative dipyridamole-thallium-201 images that increase the accuracy of the test in detecting patients at risk for ischemic cardiac complications of vascular surgery.

METHODS

Patient identification: Patients were identified retrospectively from the records of our cardiac nuclear laboratory where they had been studied from May 1983 until February 1987. The original group of 200 patients has been reported previously.¹¹ Any patient whose surgery was postponed on the basis of the thallium study was excluded. Of the 200 original patients, 82 had redistribution. Of these, all 62 whose thallium images were available for repeat analysis form the basis for this report. No patient had left bundle branch block or ventricular pacing. The 62 patients reported here were similar to the larger group previously reported, both clinically and in their perioperative cardiac event rates (17 of 62 or 27% vs 25 of 82 or 30%). Only 5 events (4%) occurred in the 118 patients without redistribution.

The patients are listed in Table I. Surgical procedures included aorto-femoral bypass grafting in 23 patients, peripheral vascular repair in 23 and abdominal aortic aneurysm resection in 16.

Dipyridamole-thallium-201 testing: Dipyridamole-thallium-201 imaging was performed using a standard protocol.^{7,11} Briefly, each patient was given 0.56 mg/kg of intravenous dipyridamole (Boehringer-Ingelheim, investigative exemption number 19,728) over 4 minutes, followed by 2 to 3 mCi of thallium-201 at 10 minutes

TABLE I Clinical Characteristics of the Study Group

	Total n = 62	Event-Free n = 45	Event n = 17	
	Raw (%)	Raw (%)	Raw (%)	p Value
Age (yrs)	67 ± 9	67 ± 10	69 ± 9	NS
Male sex	45 (73)	31 (69)	14 (31)	NS
Angina pectoris	22 (35)	14 (64)	8 (36)	NS
Myocardial infarction	11 (18)	10 (91)	1 (9)	NS
Heart failure	3 (5)	3 (100)	0 (0)	NS
Diabetes mellitus	15 (24)	9 (60)	6 (40)	NS
Systemic hypertension	40 (65)	29 (73)	11 (28)	NS
Total		73%		

Systemic hypertension defined as present in patients so diagnosed by their regular physician.
NS = not significant.

and imaging at 14 to 16 minutes. Fifty to 100 mg of aminophylline was administered by vein after the first image. The tests were supervised by a cardiologist who assessed for symptoms, blood pressure, heart rate and electrocardiographic changes. Ischemic electrocardiographic changes were defined as ≥ 1 mm of horizontal or downsloping ST-segment shift in ≥ 2 adjacent leads where baseline abnormalities did not preclude interpretation. Initial planar thallium-201 imaging was performed in 3 standard views (anterior, left anterior oblique and lateral). Delayed images were obtained after an average of 3 hours. Patients were not restricted

with respect to eating or activity in between initial and delayed imaging.

Thallium studies were scored on a semiquantitative scale by consensus of 2 experienced observers (JRL and KAE) blinded to patients' outcomes. Each standard view was divided into 5 segments and each segment was scored independently as the following: normal; uninterpretable; persistent defect with no residual thallium; persistent defect with residual thallium; partial redistribution; and complete redistribution (Figure 1). Segments with persistent defects were subdivided in view of recent studies suggesting that they may reflect ischemic myocardium in some cases.^{12,13}

Each myocardial segment was also assigned to a coronary territory, except for apical segments where the high variability of coronary supply precludes certainty. Other segments were assigned as follows: anterolateral, septal and anterior segments: left anterior descending coronary artery; posterolateral segment: left circumflex coronary artery; inferior and inferoposterior segments: right coronary artery (Figure 1).

Thallium-201 images were also scored for reversible or persistent left ventricular dilation and for abnormal lung uptake of thallium-201 defined as previously reported.^{14,15}

Postoperative cardiac events: Hospital records were reviewed without knowledge of thallium results or clinical risk factors. Ischemic cardiac events were defined as follows: unstable angina; ≥ 2 episodes of ischemic electrocardiographic changes with cardiac symptoms or signs and with subsequent resolution; ischemic pulmonary edema; acute or subacute pulmonary congestion with ischemic electrocardiographic changes; myocardial infarction; peri- and postoperative electrocardiographic and/or clinical evidence of infarction with typical cardiac enzymes; and cardiac death (sudden death or death directly attributable to myocardial infarction or congestive heart failure).

Data analysis: Clinical and thallium imaging variables were examined for association with any 1 or more of the 4 ischemic events listed before. Chi-square and Fisher's exact tests were used for dichotomous variables and Student's *t* tests were used for continuous variables. Variables associated with outcome that had a *p* value ≤ 0.1 were selected for multivariate analysis using stepwise logistic regression (BMDP Statistical Software). Differences were considered significant when *p* values were < 0.05 .

RESULTS

Overall surgical outcome: Forty-five patients had no complications (73%; group I). The other 17 patients (27%) had complications, including cardiac death in 4, myocardial infarction in 6, ischemic pulmonary edema in 4 and unstable angina pectoris in 11 (group II). The clinical findings are listed in Table I while specific cardiac events are listed in Table II. Outcome correlated neither with preoperative clinical markers (Table I) nor with the operative procedure performed.

Dipyridamole-thallium-201 test results: The thallium findings in groups I and II are listed in Table III.

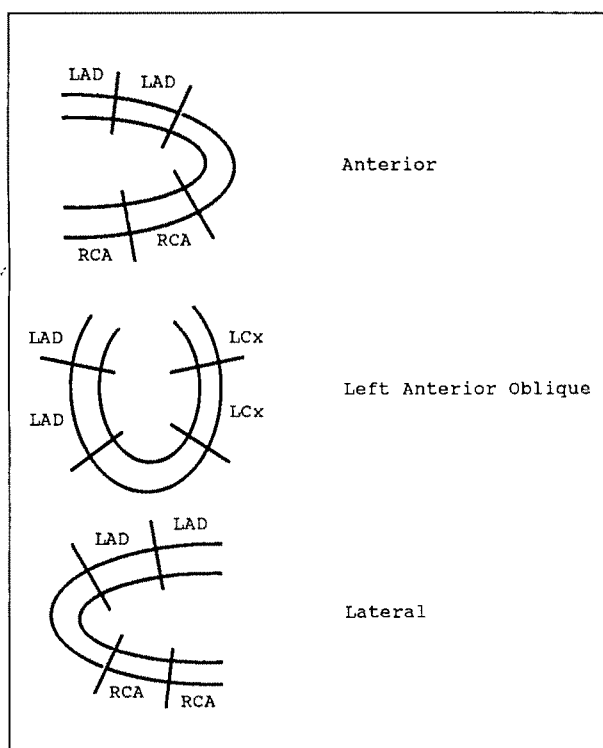


FIGURE 1. Myocardial segments for thallium-201 redistribution in 3 standard views. Coronary assignments are shown. Apical segments in each view are not assigned to any coronary distribution. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

TABLE II Age, Sex, Thallium Results and Outcomes in Patients with Cardiac Complications

Patient No.	Age (yr) & Sex	Lung Uptake	LV Dilation	Segments with RD	Views with RD	Territories with RD	Outcome
4	58M	Normal	Fixed	5	2	2	IPE/MI
5	5M	Normal	Reversible	11	3	3	A/IPE/MI
19	75M	Increased	Reversible	6	3	2	UA
20	76F	Normal	Reversible	8	3	3	UA
31	81M	Normal	Reversible	5	3	2	UA
32	75M	Normal	Fixed	11	3	3	UA
35	72M	Increased	Reversible	8	3	3	IPE/MI/D
38	74M	Normal	Absent	4	2	1	UA
39	72M	Normal	Reversible	7	3	2	UA
40	67M	Increased	Fixed	10	3	3	UA/D
42	49M	Normal	Fixed	3	2	2	MI
44	68F	Increased	Absent	8	2	2	MI/D
45	68M	Increased	Fixed	6	2	1	UA
46	69M	Normal	Absent	2	2	1	UA
47	67F	Normal	Absent	2	2	1	IPE
49	65M	Increased	Absent	4	2	2	MI/D
54	81M	Normal	Absent	4	3	1	UA

D = death; IPE = ischemic pulmonary edema; LV = left ventricular; MI = myocardial infarction; RD = redistribution; UA = unstable angina.

TABLE III Results of Dipyridamole-Thallium Testing

	Total n = 62 Raw (%)	Event-Free n = 45 Raw (%)	Event n = 17 Raw (%)	p Value Fisher Univariate	p Value Multiple Regression
Chest pain with test	19 (31)	12 (63)	7 (37)	NS	
Ischemic ECG with test	12 (19)	8 (67)	4 (33)	NS	
Fixed LV dilation	13 (21)	8 (62)	5 (38)	NS	
Reversible LV dilation	13 (21)	7 (54)	6 (46)	NS	
Increased lung uptake	11 (18)	5 (45)	6 (55)	NS	
≤3 segments with RD	25 (40)	22 (88)	3 (12)	0.03	NS
>4 segments with RD	37 (60)	23 (62)	14 (38)		
1 view with RD	15 (24)	15 (100)	0 (0)		
2 views with RD	22 (35)	14 (64)	8 (36)	0.005	<0.001
3 views with RD	25 (40)	16 (64)	9 (36)		
1 coronary zone with RD	32 (52)	28 (88)	4 (13)		
2 coronary zones with RD	23 (37)	15 (65)	8 (35)	0.007	0.015
3 coronary zones with RD	7 (11)	2 (29)	5 (71)		
Total		73%	27%		

ECG = electrocardiogram; LV = left ventricle; NS = not significant; RD = redistribution of thallium.

Dipyridamole provoked chest pain in 19 patients and ischemic electrocardiographic changes in 12 patients. These findings did not discriminate group I from group II patients. Similarly, neither fixed nor reversible left ventricular dilation was associated with cardiac complications. Increased lung uptake of thallium was noted in 11 patients (18%), of whom 5 (45%) were in group I and 6 (55%) were in group II. This difference was not significant. Similarly, there was no association between either total perfusion defects or persistent defects and outcome.

In contrast, the extent of thallium redistribution, whether assessed as the number of views, number of segments or number of coronary territories, was related to outcome (Table III). Of 37 patients with ≥4 segments showing redistribution, 14 (38%) had events, compared with only 3 of 25 patients (12%) with ≤3 such segments ($p = 0.03$). Cardiac events in the 3 patients with ≤3 segments with redistribution were limited to ischemic pulmonary edema in 1, unstable angina

in the second and myocardial infarction in the third, with no deaths. Interpretation of thallium images based on 3 instead of 5 segments per image or on a 3-point instead of a 5-point scale for perfusion did not change the association between extent of redistribution and cardiac events.

Of 47 patients with redistribution in 2 or 3 views, 17 (36%) had group II outcomes compared with none of 15 patients with redistribution in 1 view ($p = 0.005$). Of 30 patients with redistribution in 2 or 3 coronary territories, 13 (43%) had group II outcomes, compared with only 4 of 32 patients (13%) with redistribution in a single territory ($p = 0.007$). Cardiac events in the 4 patients with redistribution in only a single coronary territory were limited to ischemic pulmonary edema in 3 patients and unstable angina in the fourth (Table II).

Predictive accuracy: Multiple stepwise logistic regression analysis of the univariate clinical and scanning predictors identified thallium redistribution in >1 view ($p < 0.001$) as the strongest predictor of perioperative

cardiac events. After accounting for multiple views with redistribution, only redistribution in >1 coronary territory remained significant ($p = 0.015$). Accordingly, in these 62 patients with redistribution, there were 17 cardiac events, including 7 patients with myocardial infarction and/or death. A modified analysis requiring redistribution in 2 views would have identified a high-risk subset of 47 patients and would have missed no patient with an ischemic complication. An interpretation requiring redistribution in >1 view and >1 coronary zone would have identified only 35 patients and missed 5 patients with complications, including 4 with unstable angina pectoris and 1 with ischemic pulmonary edema, but would have missed no patient with myocardial infarction or cardiac death.

DISCUSSION

We have applied a simple semiquantitative scoring scheme to preoperative dipyridamole-thallium-201 scans. Each scan was assessed for lung uptake of thallium, left ventricular dilation and regional perfusion on a semiquantitative scale. Segments with redistribution were also assigned to likely coronary territories. Our scoring scheme was easy to use and required no special equipment.

Through the application of this scheme, we have shown that the predictive value of thallium imaging can be improved by analyzing not just for redistribution, but for the number of segments, views and coronary territories with redistribution. Patients with redistribution in ≤ 3 segments were much less likely than patients with ≥ 4 such segments to suffer a perioperative cardiac event (12 vs 38%). Patients with redistribution in only 1 view were much less likely than patients with 2 or 3 such views to have an event (0 vs 36%). In fact, no patient with redistribution in a single view had any cardiac complication of vascular surgery. Finally, patients with thallium redistribution in only 1 coronary territory were less likely than patients with redistribution in 2 or 3 territories to have a perioperative cardiac event (13 vs 43%). These observations are similar to studies which showed that a single segment with redistribution had limited prognostic value and to recent work in which the extent of dipyridamole-induced thallium redistribution was correlated with operative outcome in noncardiac surgery.^{9,16,17} The study of Lette et al,¹⁷ which was similar in intent to our own, used a more complex algorithm to create indexes of thallium abnormality. Also, their patients were characterized by a much higher risk, with perioperative cardiac death or myocardial infarction in 9 of 21 (42%) patients with redistribution, compared with only 7 of 62 (11%) in our patients.¹⁷

There are 2 possible explanations for the associations we have shown between extent of thallium redistribution and outcome after vascular surgery. One is that patients with more redistribution might be less likely to have an artifactually abnormal scan. There are many technical artifacts to which dipyridamole-thallium-201 imaging is prone.¹⁸ Image attenuation from breast or diaphragm may simulate a regional defect. The left ventricular apex may be normally thin and simulate a fixed

defect. Subtle changes in patient positioning between initial and delayed images in a single view may simulate redistribution. By requiring that redistribution be evident in 2 views to diagnose an important thallium-201 abnormality, the impact of such artifacts is minimized by using what is essentially an internal control for reproducibility.

Alternatively, patients with more redistribution might have a greater ischemic burden. While we cannot discriminate clearly between these possibilities, a deliberate effort was made not to call defects with even a low probability of being artifactually abnormal. We suspect, therefore, that the correlation between extent of redistribution and surgical complications reflect a measure of increased myocardium at risk or more severe coronary disease. Further credence to this interpretation comes by analogy from studies in which constant ischemia has been shown to relate to prognosis after myocardial infarction, whether such ischemia is measured by coronary angiography,¹⁹ electrocardiography,²⁰ or thallium-201 redistribution.²¹ Our data are also analogous to exercise thallium studies in which extent of redistribution correlated with prognosis.^{14,16,18,22}

One limitation of our study is that the original thallium interpretation was available to physicians before surgery. This knowledge would presumably have led to greater caution in patients with redistribution, decreasing the number of complications in such patients. Also, we did not use tomographic analysis, as such equipment was not available. Computer quantitative analysis was not used, primarily because its utility in dipyridamole-thallium-201 scanning has not been shown clearly. Finally, a wall motion analysis was not available and as a result the left ventricular ejection fraction was not assessed in this study.

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Management of Complications Associated with a First-Generation Endocardial Defibrillation Lead System for Implantable Cardioverter-Defibrillators

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An automatic cardioverter-defibrillator could be implanted using an endocardial defibrillation lead system (consisting of a tripolar defibrillation electrode catheter in conjunction with an epicostal patch electrode) in 9 of 10 patients with sustained ventricular tachycardia or ventricular fibrillation. Six lead system complications were observed during a follow-up period of 51 ± 36 weeks. Three catheter electrode conductor fractures occurred and manifested as oversensing and subsequent delivery of inappropriate shocks (1 patient), inability to defibrillate during electrophysiologic testing 3 months after implant (1 patient) and sudden cardiac death (1 patient). Asymptomatic patch electrode conductor fractures were detected on a routine chest roentgenogram in 2 patients. Endocardial defibrillation threshold testing performed at the time of implantation resulted in malfunction of a previously implanted permanent pacemaker pulse generator in 1 patient. Catheter and patch electrode replacement procedures were performed in 3 consenting patients under local anesthesia. Endocardial defibrillation thresholds after lead replacement were comparable to those obtained at time of initial implant. Serial clinical, roentgenographic and electrophysiologic evaluation should be included in follow-up procedures for endocardial defibrillation lead systems. Monitoring for deleterious effects of endocardial defibrillation threshold testing on previously implanted pacemaker systems should be performed at the time of implant and during follow-up. Improved lead designs are necessary for long-term use of endocardial defibrillation electrodes, but replacement procedures are feasible without thoracotomy.

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The automatic implantable cardioverter-defibrillator has been approved for use since 1985 in the treatment of drug-refractory sustained ventricular tachycardia/ventricular fibrillation and in survivors of sudden cardiac death who have a significant risk of recurrence. In uncontrolled studies, long-term arrhythmic mortality in patients with implantable cardioverter-defibrillators is greatly diminished.¹⁻³ However, device and lead system insertion is associated with significant morbidity and mortality,⁴ largely related to a thoracotomy that is required for placement of 1 or more epicardial electrodes. This greatly decreases patient and physician acceptance of this therapy and also limits its usefulness in patients who are poor surgical candidates or who have had prior or anticipate possible future thoracic surgical procedures. Endocardial defibrillation lead systems are currently under investigation. Implantation of a cardioverter-defibrillator with such a lead system and successful defibrillation was reported in 1988.⁵ We attempted implant of this endocardial defibrillation lead system in conjunction with a cardioverter-defibrillator without thoracotomy in 10 patients with ventricular tachycardia/ventricular fibrillation. We have observed a number of lead system complications both at the time of implant and during follow-up. In this report we examine the clinical presentation, diagnosis and management of complications of this endocardial defibrillation lead system.

METHODS

We used a tripolar endocardial cardioversion-defibrillation electrode catheter (Endotak®-C, Cardiac Pacemakers, Inc. [CPI]) in conjunction with a subcutaneous implantable patch electrode (Endotak-SQ, CPI) and an automatic implantable cardioverter-defibrillator (Ventak® AICD, CPI). The electrode catheter has dual spring defibrillation electrodes and a distal tip sensing electrode incorporated into a silicone rubber, tined-tip catheter. Cardioversion-defibrillation is accomplished through the 2 spring electrodes, which are separated by a length of silicone rubber insulation. The spring electrodes are platinum-coated titanium ribbons coiled into a helix around the body of the catheter. The distance from the catheter tip to the proximal spring electrode is variable (10 to 16 cm) and allows for correct positioning of the 2 defibrillation electrodes in patients with different cardiac chamber dimensions. Rate-sensing electro-

TABLE I Clinical Characteristics of Patients Who Underwent Implantation of Endocardial Lead System

Patient No.	Age yrs & Sex	Diagnosis	LVEF (%)	Implant Date	Surgeon	Discharge Meds	Follow-Up (weeks)
1	69, M	VT-S, CAD	20	3/2/87	1	0	17
2	70, M	VT-S, CAD, CABG	30	3/24/88	3	PA	91
3	59, M	VT-S, CAD, CABG	35	4/15/88	1	0	88
4	65, M	VT-S, CAD	21	4/15/88	2	—	1
5	60, M	VT-CAD, CABG	46	6/30/88	3	Mexiletine	78
6	72, M	VT-S, CAD	41	7/8/88	2	Amiodarone	77
7	70, M	VT-S, CAD, CABG	46	7/20/88	3	Quinidine	75
8	51, F	SCD, CAD, CABG	45	10/17/88	3	Metoprolol	13
9	66, M	VT-S, CAD, CABG	32	10/21/88	3	PA	11
10	69, M	VT-S, CAD, CABG	42	11/7/88	3	PA, propranolol	62

Abbreviations: CABG = status post coronary artery bypass graft; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; Meds = medications; PA = procainamide; SCD = survivor of sudden cardiac death; VT-S = sustained ventricular tachycardia.

cardiograms are obtained from a porous, platinum-iridium tip electrode positioned in the right ventricular apex and the distal spring electrode. The conductor wires are helical drawn braided strand wires wound in a spiral coil. The lead body contains separate lumina for each of 3 sensing and shocking conductor wires as well as for a stylet used during implantation. Each conductor wire is welded to a titanium connector pin protruding from the proximal end of the electrode catheter. The patch electrode consists of a platinum-iridium wire mesh laminated between 2 Dacron-reinforced silicone rubber sheets. The connector wire is also a double helical drawn braided strand coil contained in a silicon rubber catheter body.

We implanted the patch electrode in an epicostal position over the left thoracic wall and used it in conjunction with the Endotak-C lead.⁵ The patch and the 2 spring electrodes constitutes a tripolar electrode system and may be used to deliver either unidirectional or bidirectional shocks.

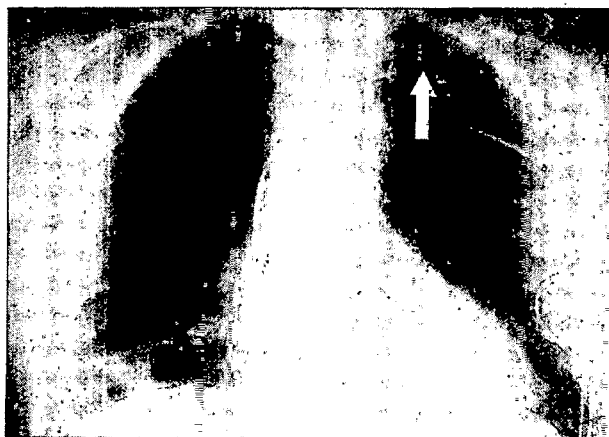


FIGURE 1. Endocardial lead fracture. The chest roentgenogram shows the triple electrode endocardial cardioversion-defibrillation lead which is inserted via the left subclavian vein. The proximal spring electrode can be seen as a thickening of the lead at the level of the right atrium-superior vena cava junction. The distal spring electrode is located in the right ventricle. The shadow of the submuscular patch electrode can be seen at the left edge of the thoracic wall. A connector coil fracture is present in the lead at the point beneath the clavicle where it enters the subclavian vein (arrow). The lead appears to be bent proximal to this fracture.

Ten patients underwent attempted implantation of the endocardial system in conjunction with an implantable cardioverter-defibrillator at our institution. Clinical characteristics of these patients are listed in Table I. All patients had either spontaneous ventricular tachycardia/ventricular fibrillation or were survivors of sudden cardiac death. There were 9 men and 1 woman, mean age 65 ± 7 years (range 51 to 72). All patients had coronary artery disease and 7 patients had undergone previous coronary artery bypass surgery. Mean left ventricular ejection fraction was $36 \pm 10\%$. Each patient had undergone baseline electrophysiologic testing. All patients were either refractory to medical therapy as demonstrated by serial drug testing, or drug efficacy could not be assessed because of non-inducibility at baseline. Patients undergoing serial drug testing failed a mean of 5 antiarrhythmic drugs (range 2 to 8). Lead system implantation was performed under general anesthesia (9 patients) or local anesthesia with intermittent sodium pentobarbital general anesthesia for defibrillation threshold testing (1 patient). The endocardial electrode catheter was inserted into the left subclavian vein through a 12Fr peel-away introducer sheath and positioned such that the tined tip was wedged into the right ventricular apex. Proper selection of catheter size allowed the distal spring electrode to be located within the right ventricular cavity and the proximal spring electrode to be located at the junction of the right atrium and the superior vena cava. The body of the lead was secured with non-absorbable suture material to the pectoralis fascia and tunneled along the left thoracic wall to a subcutaneous pocket in the left upper quadrant, where the pulse generator would be positioned. Various dual and triple electrode configurations were then randomly tested for endocardial defibrillation threshold.

A temporary cutaneous patch electrode (R2®, Darox Corp.) was used to map various chest wall positions to determine optimal patch position, yielding the lowest defibrillation threshold. A triple electrode configuration was used and consisted of the distal spring electrode serving as the cathode and the proximal spring electrode connected to the cutaneous patch electrode serving as dual anodes. The dual anodes were connected using a Y-connector (Endotak-Y Model 5834, CPI). Once optimal patch position was determined, the subcutaneous patch electrode was implanted epicostally at this site.

This patch electrode was connected to the Y-connector in place of the previously tested cutaneous patch electrode and the defibrillation threshold was rechecked using the implanted lead system. An implantable cardioverter-defibrillator pulse generator was then connected to the leads and tested for proper functioning. Proper function of the implanted cardioverter-defibrillator system was determined by documenting successful termination of induced ventricular fibrillation with the first shock from the pulse generator on 2 successive inductions. This was documented at the time of implant and before discharge. Patients were followed monthly after discharge and routine electrophysiologic evaluation and cardioverter-defibrillator system testing was performed 9 to 15 (mean 12) weeks after implant.

RESULTS

Six complications related to the endocardial lead system have been observed over a follow-up period ranging from 0 to 21.5 months. These complications involved the endocardial cardioversion-defibrillation electrode catheter (3 patients), the subcutaneous patch electrode (2 patients) and a previously inserted permanent pacemaker pulse generator (1 patient). The permanent pacemaker interaction occurred at implant and the remainder occurred 10 to 46 weeks after implant. Postoperative endocardial lead system complications presented as sudden death (1 patient), multiple inappropriate defibrillator discharges (1 patient), failure to defibrillate at the time of follow-up electrophysiologic examination (1 patient), or were detected on radiologic examination before symptoms (2 patients).

Endocardial electrode catheter complications:

Three patients had catheter electrode complications. Patient 9 presented with sudden death 11 weeks after implantation. In addition to the cardioverter-defibrillator, he had a permanent Astra T6 pacemaker (CPI) inserted at the time of defibrillator implant. The active-fixation pacemaker lead was positioned at the right ventricular outflow tract to minimize interaction between

pacemaker and defibrillator leads. Electrophysiologic testing at implant and before discharge demonstrated normal functioning of both devices. This patient experienced "static electric shock" sensations 11 weeks after implant, and contacted his primary physician. He expired the same night before evaluation by his physician. A postmortem chest radiograph showed coil fracture just internal to the site of entry into the subclavian vein. Postmortem examination of the endocardial electrode catheter revealed a focal area of charring of the connecting wire coils inside of the catheter body up to 2 or 3 cm inside the subclavian vein entry site. Microscopic examination suggested fusion of the coils. Pulse generator interrogation revealed that 38 device discharges were delivered since his previous evaluation. Either ineffectual shock delivery in response to ventricular tachycardia/ventricular fibrillation or inappropriate shocks initiating ventricular tachycardia/ventricular fibrillation were considered responsible for the "sudden" death.

Patient 3 experienced multiple inappropriate shocks after the strenuous use of his left arm. Pulse generator interrogation confirmed that 7 shocks were delivered. Application of a magnet to the pulse generator resulted in the emanation of erratic audio tones that were not synchronous with the QRS complex. A chest x-ray revealed marked lead redundancy with fracture of the endocardial electrode catheter at the subclavian vein entry site (Figure 1). Lead discontinuity was documented by recording signals from the rate-sensing electrodes of the endocardial lead. The endocardial lead was successfully removed and replaced under local anesthesia.

The cardioverter-defibrillator failed to defibrillate induced ventricular fibrillation in patient 8 during a routine 3-month follow-up electrophysiologic study. The patient had been asymptomatic and had not experienced defibrillator discharges after implant. Chest x-ray revealed retraction of the endocardial lead by approximately 5 cm with a stretched appearance of the conductor in the superior vena cava. Unipolar recordings from the proximal spring electrode documented an open cir-

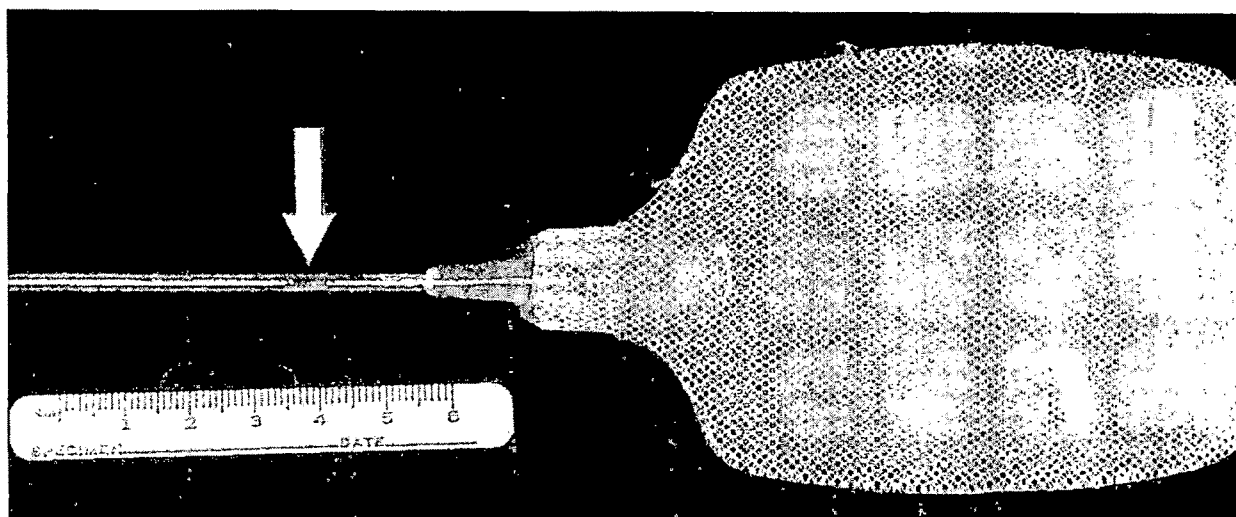


FIGURE 2. Patch electrode fracture. The photograph reveals a patch electrode that was explanted from Patient 2. Discontinuity of the connector coil can be seen approximately 1 cm from the junction of the patch and the body of the lead after application of slight traction (arrow).

cuit with no measurable signal and lead impedance near infinity. Thus, failure to defibrillate was related to the delivery of a unidirectional shock rather than a bidirectional shock. Attempts to remove the endocardial lead were unsuccessful and the patient opted to receive amiodarone.

Subcutaneous patch electrode complications: Two patch electrode complications were observed. These were coil fractures detected on routine chest x-ray in patients 2 and 6. They were detected at 46 and 30 weeks after implant respectively. One fracture was positioned at the junction of the body of the lead and the patch, and the other fracture occurred 2 cm proximal to the patch-lead body junction (Figure 2). Unipolar recordings documented an open circuit in both cases (Figure 3). In both cases the patch was successfully removed and replaced under local anesthesia.

Complications related to defibrillator-pacemaker interaction: Irreversible malfunction of an implanted cardiac pacemaker pulse generator occurred during implant of an endocardial lead system (1 patient). An Activitrax® pacemaker (Medtronic, Inc.) was previously implanted along with a bipolar endocardial lead located at the right ventricular apex. The endocardial defibrillation electrode catheter was also positioned at the apex 1 to 2 cm from the pacemaker lead. At the time of defibrillation threshold testing, both endocardial and trans-thoracic direct current shocks were delivered. Subsequently, the pacemaker pulse generator failed to emit output pulses in response to asystole and after application of a magnet. Temporary transvenous pacing was emergently instituted and the damaged pulse generator was explanted. The pacemaker pulse generator was im-

mediately replaced and the pacemaker lead was repositioned several centimeters from the endocardial defibrillation lead.

DISCUSSION

We report 6 complications of endocardial defibrillation lead systems. Five of these involve lead system failure and 1 could represent an endocardial lead system/permanent pacemaker system interaction. Though the presentation of post-implant endocardial lead system failure varied in our series, it can be classified into 3 categories: (1) oversensing resulting in inappropriate shocks, (2) failure of cardioversion-defibrillation (ineffective shocks) and (3) "asymptomatic" lead fractures. A lead fracture can be asymptomatic in sinus rhythm if it does not involve the rate-sensing electrodes but can result in ineffective defibrillation. An open circuit in rate-sensing electrodes results in undersensing of ventricular tachycardia/ventricular fibrillation while intermittent noise-sensing may lead to inappropriate shocks.

Sudden death in patient 9 may be due to an inappropriate shock that induced ventricular fibrillation, an ineffective shock (the defibrillator actually registered 38 delivered shocks), or both. All lead system failures appeared to be related to connector coil disruption with fracture or arcing, or both, between the coils due to insulator breakdown. In other patients we have noted progressive stretching of the conductor coil with increasing lead redundancy along the left thorax. Similar complications are less common with epicardial lead systems and a total incidence of 0.9% has been reported.⁶ Endocardial defibrillator lead conductors have more potential stress sites since the lead body courses through the sub-

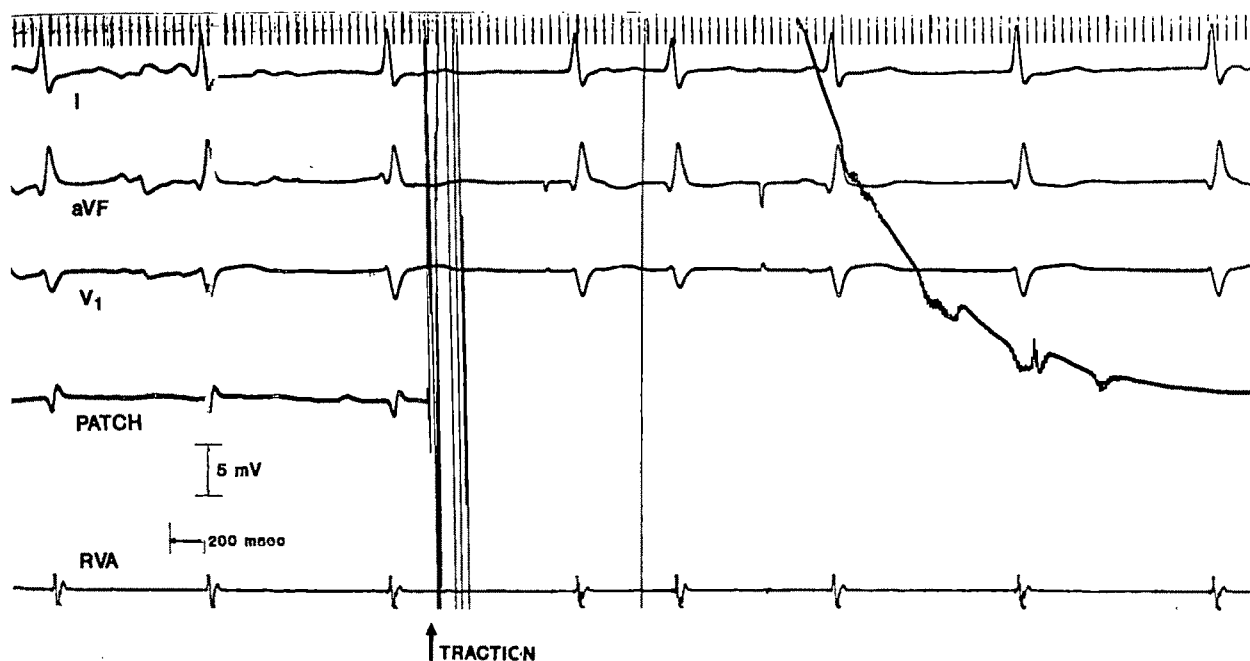


FIGURE 3. Electrophysiologic recording of signal discontinuity in a patch electrode fracture. Surface electrocardiographic leads I, aVF and V₁ and a unipolar recording from the patch electrode are simultaneously recorded along with a bipolar recording from a multielectrode catheter placed at the apex of the right ventricle. Gentle traction was applied to the lead body as it emerged from the open defibrillator pocket (arrow). Instantaneous loss of the signal and large-amplitude noise can be seen, demonstrating intermittent discontinuity of the patch electrode conductor coil. mV = millivolts (recorded from the patch electrode); RVA = right ventricular apex.

cutaneous tissues along the left chest wall and must withstand the stress of physical activity. The drawn braided strand double helical coil conductor wire design used in this lead system may be unsuitable for this purpose. Also, the large diameter of the endocardial lead may be subjected to excessive pressure in the subclavian vein due to space limitations between the clavicle and the first rib. Thus, large size, multi-electrode catheters may be undesirable for single site insertion via the subclavian vein. While similar complications have been reported for dual chamber pacing lead systems, these are infrequent and use of separate entry sites may reduce this risk.⁷ Separate lead bodies can decrease insulation breakdown and arcing in a single catheter.

Because of their varied clinical presentation and because asymptomatic lead system failures can occur, periodic evaluation of lead system integrity is mandatory. Such evaluation should include a detailed history of events and symptoms as well as examination of magnet audiotapes for a nonprogrammable cardioverter-defibrillator. Lead system failure should be suspected if a history of sudden change in pattern of defibrillator discharges is elicited. This includes frequent single discharges in a short time period or multiple discharges during a single event in a patient with previously acceptable defibrillation thresholds. Routine posteroanterior and lateral chest roentgenograms are necessary to detect asymptomatic connector coil fractures. Electrophysiologic study should be performed to document the proper function of the system. Indeed, electrophysiologic studies may be a necessary part of routine follow-up to detect lead system failures that may pass unnoticed on x-ray examination.

It is unclear whether the endocardial shock or the transthoracic rescue shock used during defibrillation threshold testing in patient 4 was responsible for pacemaker pulse generator damage. External and internal defibrillation can cause pacemaker dysfunction. Until implantable defibrillators with demand bradycardia pacing become more widely available, interaction between permanent pacemakers and endocardial defibrillation shocks will be important. Both lead systems should be at disparate locations. Additionally, proper pacemaker function and programming should be documented after endocardial defibrillation testing and after spontaneous defibrillator discharges. Though a large number of endocardial defibrillation leads in this report subsequently developed failures, replacement of an endocardial lead was accomplished in 1 patient and replacement of the patch electrode was accomplished in 2 patients. All lead replacements were performed under local anesthesia, and the defibrillation threshold of the replacement lead system was not significantly different

from the defibrillation threshold at the time of the original implant. In contrast, replacement or removal of epicardial lead systems requires extensive, complicated surgery and general anesthesia.

Future endocardial defibrillation lead systems should give due consideration to potential complications. Use of separate atrial and ventricular leads and extension leads from the subclavian entry site to the pulse generator pocket may simplify lead replacement procedures. Also, separate atrial and ventricular leads allow for individual atrial and ventricular sensing to improve specificity of ventricular tachycardia/ventricular fibrillation detection and permit dual chamber pacing.⁸ Electrocardiogram telemetry and lead impedance measurements would enable the physician to noninvasively evaluate the lead system integrity before significant complications arise.⁹ Alternatives to patch electrodes can include wire or catheter electrodes.¹⁰ A small caliber, flexible pacing-defibrillation catheter electrode has been described.¹⁰ Successful placement and defibrillation have been demonstrated with this system. It must be emphasized that the complications of individual endocardial defibrillation lead systems can be expected to be specific in some instances to each model and each future system will need to be evaluated for generic and individual problems.¹¹

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Characteristic Variation in Evoked Potential Amplitude with Changes in Pacing Stimulus Strength

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The evoked potential, the intracardiac signal generated by a pacing stimulus, shows promise as a sensor for rate-responsive pacing and automatic threshold determinations. Thus, it is important to understand factors that may alter the morphology of evoked potentials and affect accurate signal analysis. Using a computer-based pacing system emulator, stimuli at 2.5, 5.0 and 6.9 V were delivered to 12 patients through permanent bipolar pacing leads. At 2.5 V, the evoked potential amplitude measured -12.63 ± 7.79 mV. When the pacing amplitude was increased to 5.0 and 6.9 V, the signal diminished in size or reversed in polarity, or both, averaging -0.83 ± 7.82 mV and 0.64 ± 7.0 mV, respectively ($p < 0.01$ vs 2.5 V). Pacing at 2.5 V was performed in an additional 8 patients with temporary quadripolar electrode catheters. With the distal pole of the catheter as the cathode and the proximal 3 poles as a common anode, the evoked potential averaged -9.01 ± 5.44 mV. With the proximal 2 poles of the catheter disconnected to make the anode equal in size and current density to the cathode, the evoked potential diminished to -0.94 ± 11.27 mV ($p < 0.05$). There is thus a decrease in the evoked potential at high stimulus amplitudes compared to that obtained at the cathodic threshold. This finding can be reproduced by manipulation of the size and current density of the anode, suggesting that anodal stimulation at the ring of permanent pacing leads may be responsible.

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The evoked potential is the intracardiac electrocardiogram signal generated by a pacing stimulus. The ventricular depolarization gradient, the peak negative amplitude of the integral of the evoked potential, changes with exercise, changes in heart rate and infusion of catecholamines make it useful as a sensor for rate-responsive pacing.¹ Analysis of evoked potentials could also be valuable for automatic threshold tracking. The basis of automatic threshold tracking is the introduction of pacing stimuli and analysis of the resultant stimulated electrocardiograms, or evoked potentials, for capture, noncapture and fusion. Factors that might alter the morphology of evoked potentials that are not related to alterations in physiologic rate requirements of an individual or loss of capture by pacing stimuli are thus important and must be identified.

We performed cardiac pacing on patients using a computer-based pacing system emulator to vary stimulus voltage and analyze the resultant evoked cardiac signals. In the course of this study, we found characteristic changes in evoked potentials at constant pacing rates and at stimulus amplitudes well above threshold. Such changes are due to increasing stimulus amplitude alone and reflect neither loss of capture nor changes in physiologic status that would change the gradient for rate-responsive pacing. We report a systematic investigation of this phenomenon during permanent pacemaker implantations and invasive electrophysiologic studies.

METHODS

Clinical research system: This is a portable computer-based pacing system emulator consisting of a computer, co-processor, isolation box, cables and the software to run the system. Changes in software design for pacemakers can be tested in patients using the system before implantable devices are actually built, making multiple design changes easy to accomplish. In this study, the computer system was connected to patients via sterile cables attached to the proximal ends of bipolar permanent pacing leads or electrode catheters during pacemaker implantations or electrophysiologic studies, respectively.

A triphasic stimulus waveform consisting of a precharge, stimulus and postcharge was used for pacing.^{2,3} Polarization artifact must be minimized to analyze evoked potentials accurately, and this was accomplished by optimizing precharge duration. Precharge amplitude is a nearly linear function of precharge duration, stimu-

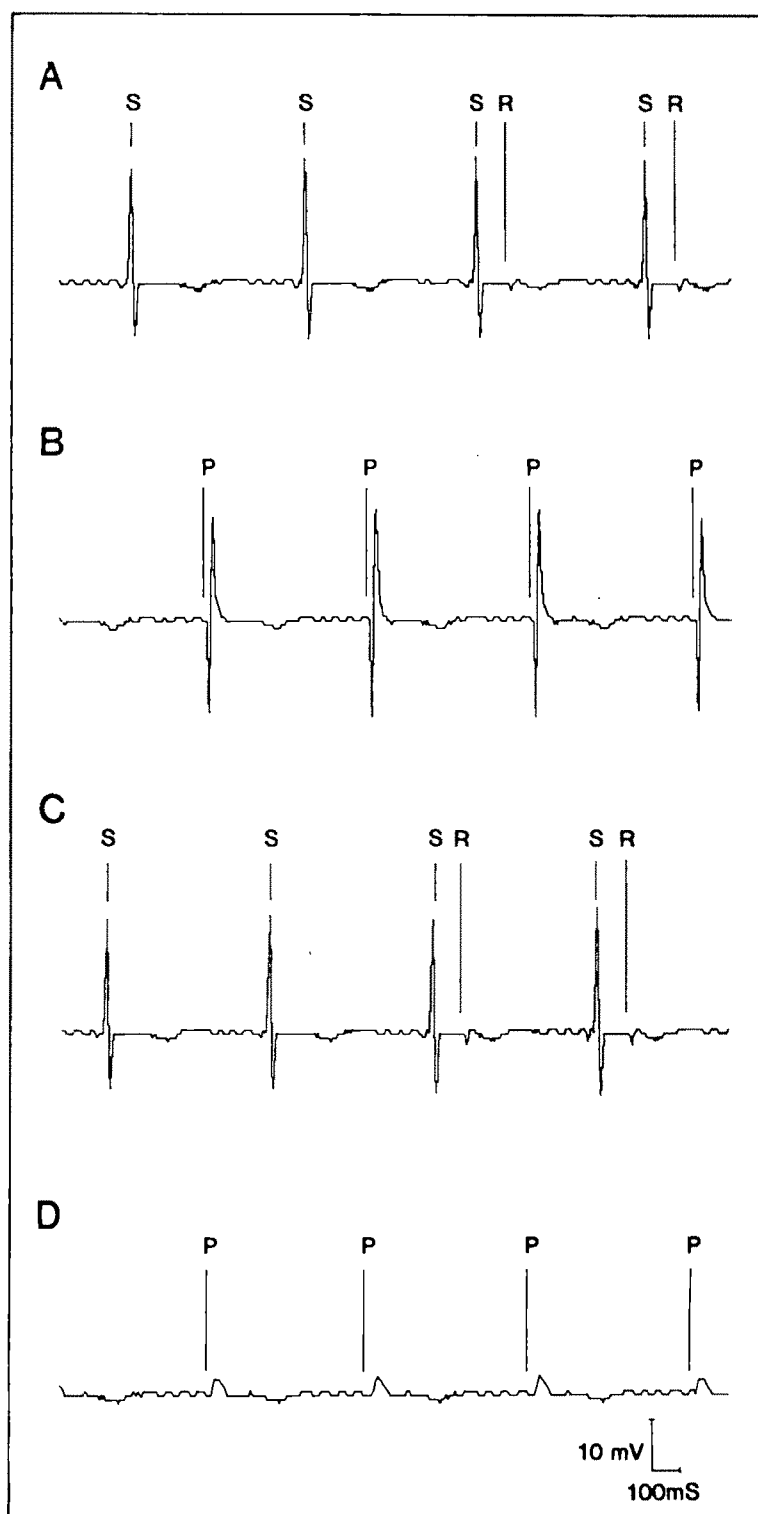
lus amplitude and lead impedance. For a 500 ohm electrode and a 3-ms pulse width, the designed precharge amplitude is 15% of the stimulus amplitude. Measured values are closer to 20%.

The optimal precharge duration was set by an automatic balancing algorithm that separated polarization artifact from the stimulated cardiac depolarization by injecting a test stimulus in the refractory period of a cardiac event (100 ms after the onset of the R wave). The polarization artifact was minimized whenever stim-

ulus amplitude was changed, except that it was balanced at 2.5 V and held constant during automatic threshold tests when amplitude was varied continuously.

Overdrive pacing was performed in each patient at a rate sufficient to eliminate fusion beats, and this pacing rate was held constant throughout the study on any one patient. Pacing amplitude was varied and the resultant evoked intracardiac signals stored in the computer for subsequent analysis. Although several measures of morphology were calculated on a realtime basis, a simple

FIGURE 1. A, permanent bipolar pacing lead. With a precharge duration of 3,456 μ s, polarization artifact is minimized when pacing stimuli are introduced during the refractory period of sensed beats. Amplitude = 2.5 V; sensitivity = 13 mV; P = paced beat; R = refractory pacing stimulus; S = sensed beat. The time scale is expanded throughout this figure to demonstrate the small size of the polarization artifact more easily. B, a large amplitude evoked potential is generated with pacing at 2.5 V. Precharge = 3,456 μ s. C, when pacing at 6.885 V, the polarization artifact is still minimal with a precharge duration of 3,456 μ s. D, at a pacing amplitude of 6.885 V, the evoked potential is smaller in amplitude and has a positive phase only.



measure of depolarization morphology, amplitude and polarity easily demonstrated the variation in the evoked potential at pacing amplitudes greater than the cathodic threshold.

Permanent pacemaker implantations: Twelve patients undergoing permanent pacemaker implantations had bipolar pacing leads advanced to the right ventricular apex using standard techniques. The threshold for pacing was tested with a standard pacing system analyzer. After optimal positioning of the lead was accomplished, it was connected to the clinical research system and the heart was paced at a rate sufficient to insure consistent capture without fusion beats at amplitudes of 2.5, 5.0 and 6.9 V each for 30 seconds, with recording of the evoked potentials. At each amplitude, polarization artifact was minimized with the balancing routine before data were collected. Some patients also were scanned through multiple stimulus amplitudes with recording of evoked responses at each amplitude.

Electrophysiologic studies: Eight patients were studied who were having routine electrophysiologic studies for standard indications and who had a quadripolar electrode catheter (Bard Electrophysiology) in the right ventricular apex. At the end of the diagnostic electrophysiology study, the electrode catheter was connected to the pacing system emulator. Stimulus amplitude was held constant at 2.5 V and the polarization artifact was minimized for that voltage. Initially the distal pole of the electrode catheter was designated the cathode and the proximal 3 poles were connected in common as the anode to achieve a large surface area, low current density anode. After 30 seconds of overdrive pacing, the proximal 2 poles of the electrode catheter were disconnected from the system, leaving the second pole of the catheter as a small surface area, large current density anode. Pacing was continued with appropriate recordings.

Signal analysis: For each recording, the amplitude of each evoked potential (in mV) was measured. The mean of 8 values from the beginning of each 30 seconds of pacing was determined, as the signals were stable and including larger numbers of signals did not affect the results. The differences in the averaged peak signal amplitudes at the various pacing amplitudes for permanent pacing leads were analyzed using Freedman's test. The change in peak signal amplitude from a large to a small surface area anode with electrode catheters was analyzed the same way. A significant difference was defined as $p < 0.05$.

RESULTS

Polarization artifact: That polarization artifact can be effectively minimized is shown in Figure 1A, in which there is minimal artifact at a 2.5 V pacing amplitude. Figure 1C shows minimal artifact as well at a 6.9 V pacing amplitude, and we were able to achieve this consistently regardless of the type of pacing lead or temporary catheter used. Evoked potentials can thus be analyzed without being obscured by polarization artifact.

Permanent pacemakers: The threshold for pacing with permanent leads averaged 0.56 ± 0.15 V. The dif-

TABLE I Permanent Bipolar Pacing Leads Used

Company	Model No.	No. of Patients
Teletronics Pacing Systems	030-284	6
Cardiac Pacemakers Inc.	4268	1
Cardiac Pacemakers Inc.	4260	1
Cordis	329-201	3
Cordis	321-558	1

TABLE II Mean Evoked Potential Amplitude at Different Stimulus Amplitudes

Amplitude (volts)	2.5	5.0	6.8
Evoked Potential, mV	-12.6 ± 7.9	-0.83 ± 7.8	0.64 ± 7.0
	$p < 0.01$	NS	
		$p < 0.01$	

NS = not significant.

ferent bipolar leads used in the study are listed in Table I. In all cases the surface area of the anode exceeded that of the cathode by a factor of at least 5 to 1.

In the 12 patients studied, there was typically a large amplitude-evoked potential when pacing at 2.5 V. The electrocardiogram averaged -12.6 ± 7.8 mV among all the patients. When the pacing amplitude was increased to 5.0 V, the evoked potential diminished in size and at times reversed in polarity, so that the mean signal amplitude was -0.83 ± 7.8 mV ($p < 0.01$). On further increase in the pacing amplitude to 6.9 V, little additional change was seen, with the signal amplitude averaging 0.64 ± 7.0 mV ($p < 0.01$ compared to 2.5 V). These results are listed in Table II. A typical example of the change in the signal seen is displayed in Figure 1.

The changes we observed occurred between the pacing amplitudes of 2.5 and 5.0 V, with no additional change beyond 5.0 V. To further characterize the phenomenon and the voltage at which the signal diminished in size, recordings were obtained on 2 patients through a range of pacing amplitudes. The transition point at which the evoked potential diminished in size could be clearly determined, and it occurred at 3.9 and 4.0 V, respectively (Figure 2).

Electrophysiologic studies: If the observed diminution in signal size were due to stimulation at the anode in addition to cathodic stimulation, then the phenomenon should be more apparent with a high current density, low surface area anode than with a low current density, high surface area anode. Accordingly, patients with quadripolar electrode catheters in the right ventricular apex were paced with the tip as the cathode and with 2 configurations of the anode. With the proximal 3 poles of the catheter as a common anode, the evoked potential was predominantly negative (Figure 3A), with a mean value of -9.0 ± 5.4 mV. With the proximal 2 poles of the catheter disconnected to make the anode equal in size and current density to the cathode, the evoked potential diminished in size, averaging -0.94 ± 11.3 mV, as shown in Figure 3B ($p < 0.05$). The threshold for pacing with these electrode catheters averaged 0.95 ± 2.9 V.

The potential effect of the diminution in signal size with increasing pacing amplitude on automatic threshold tracking is shown in Figure 4. In Figure 4C, there is a large, biphasic evoked potential at a pacing amplitude of 0.7 V, the cathodic threshold. In Figure 4D, signal amplitude decreases as pacing amplitude increases to 1.0 V. The slight beat-to-beat variation in evoked poten-

tial amplitude during the transition in signal size across this tracing may be due to intermittent contact of the ring with the endocardium; the change is quicker than would be possible with respiratory variation. In Figure 4E, the signal morphology and amplitude is so different from that at the cathodic threshold that it could be interpreted as noncapture. This diminution in signal size

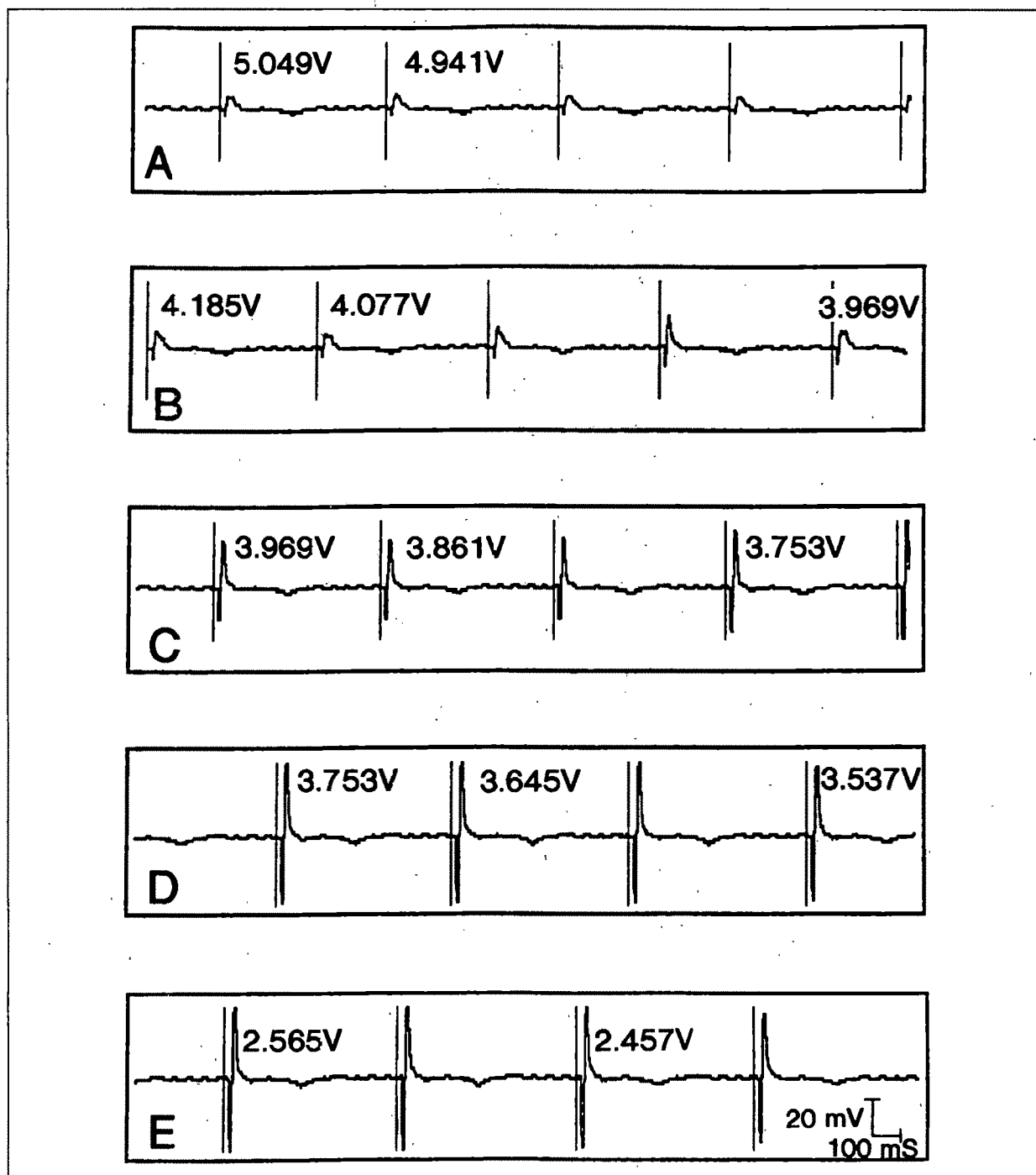


FIGURE 2. Evoked potentials were recorded continuously as pacing amplitude was gradually decreased from 5.0 V to the cathodic threshold. Polarization artifact was minimized with a precharge duration of 3,392 μ s, which was constant throughout this recording. Each panel is discontinuous, but all were recorded through the same sequence of pacing. The evoked potential has a small, mainly positive deflection at 5.0 V (A). No change is seen in the evoked potential through 4.077 V (B). At 3.969 V the evoked potential develops a predominantly negative deflection with an increase in amplitude (C). The evoked potential remains large and biphasic throughout the rest of the threshold determination (D, E).

could be avoided by connecting the 3 proximal rings together to reduce anodal current density when using quadripolar catheters.

DISCUSSION

The most important finding of this study is that there is a marked change in the magnitude of the evoked potential with increasing pacing amplitude in permanent bipolar pacing leads. We also found a comparable change in the signal recorded from electrode catheters when the current density at the anode was increased by decreasing the anodal surface area, suggesting the occurrence of anodal stimulation at the proximal electrode at high stimulus amplitudes. These findings have important implications for automatic analysis of evoked potentials for rate-adaptive pacing and threshold determinations. Factors that alter evoked potentials without reflecting true physiologic changes may lead to erroneous signal interpretation. An example is an interpretation of a small, nearly isoelectric signal as noncapture when normal pacing is still occurring.

Anodal stimulation refers to the occurrence of cardiac depolarization at the anode. This has been demonstrated in animal studies in which a series of electrodes attached to the heart allowed recording of the direction of cardiac activation to determine if it were unipolar cathodal, unipolar anodal or bipolar for a particular stimulus strength.⁴⁻⁶ Similar recordings have been made in humans using specially designed electrode catheters to allow recording of activation times near the cathode and the anode, again to determine the relative sequence of cardiac depolarization.⁷ Anodal stimulation actually occurs preferentially over cathodal stimulation during the relative refractory period, and it may be associated with an increased vulnerability to ventricular fibrillation, particularly after myocardial infarction.^{4,5,3-13}

As stimulus amplitude changes, the surface electrocardiographic signal would look the same regardless of

whether local activation in a bipolar system were unipolar cathodal or anodal or bipolar, since the overall vector of cardiac depolarization is essentially the same. On the other hand, the morphology of the sensed intracardiac signal recorded from the pacing lead could vary because of changes in the direction of depolarization depending on the sensing configuration and the source of the signal (tip or ring, or both). In our study, large negative deflections were recorded with low amplitude stimulation consistent with cathodal stimulation with the wavefront of cardiac activation spreading away from the tip. With higher amplitude stimulation, nearly isoelectric deflections were seen, which are consistent with cardiac depolarization occurring at both the tip and the ring with the wavefronts tending to cancel each other out. The threshold for anodal stimulation should be higher than for cathodal stimulation both because of intrinsic differences in these modes of stimulation and because the surface area of the anode is several times larger than that of the cathode in permanent pacing leads. In addition, apposition of the ring to the myocardium may not be as good as that of the tip. The contribution of surface area to this phenomenon is confirmed by the results with temporary electrode catheters, in that similar marked changes in the evoked intracardiac signal were seen when anodal surface area was decreased, enhancing the ability of stimulation of the anode to cause cardiac depolarization.

We have examples of diminution of the evoked potential with pacing amplitudes as low as 1.0 V in temporary electrode catheters, while the transition point was much higher in permanent pacing leads, typically greater than 3.0 V. This difference is not surprising given the relative differences in anodal current density with the 2 types of catheters.

Our observations are important for the development of analysis of evoked potentials as a physiologic sensor. Automatic threshold determination requires the design

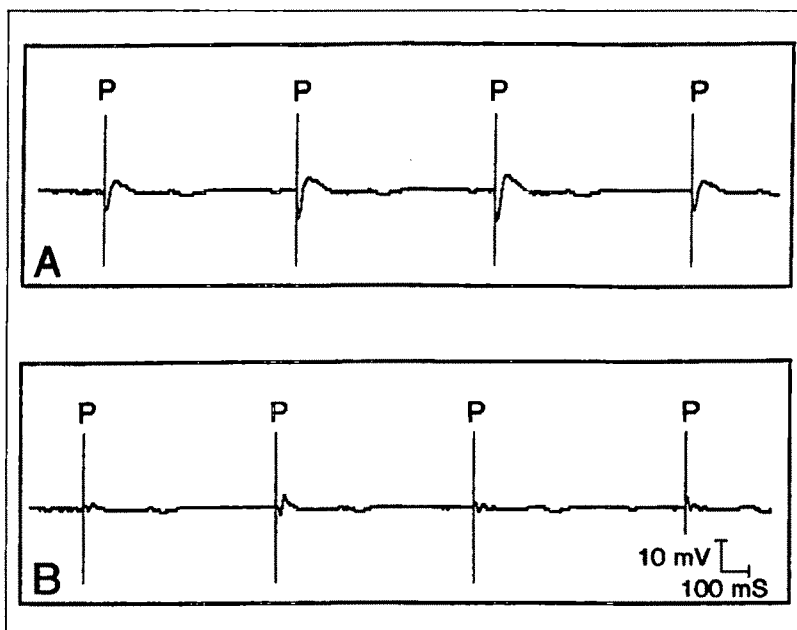
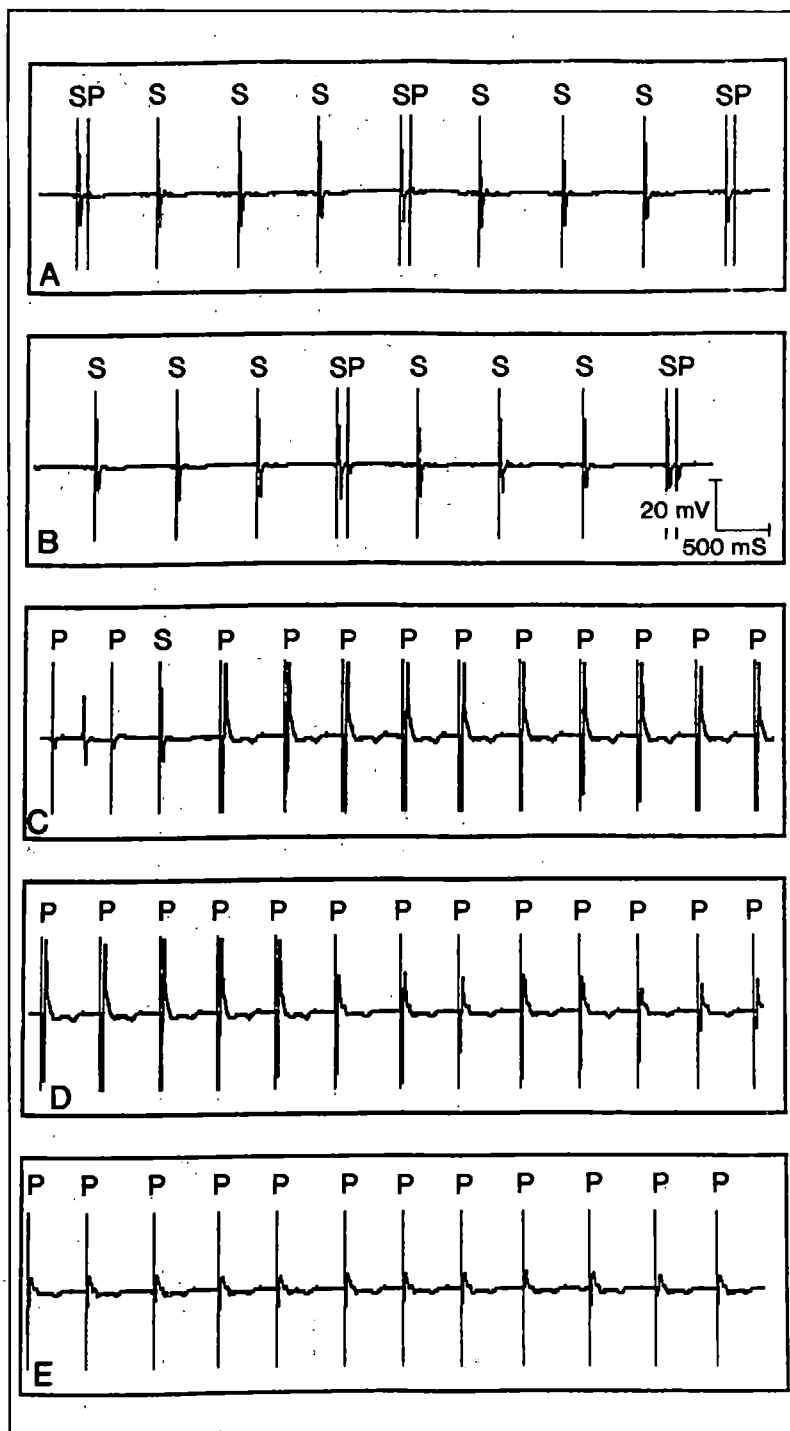


FIGURE 3. A, evoked potentials recorded from a temporary quadripolar electrode catheter with the tip electrode as the cathode and the proximal 3 electrodes as a common anode. Pace amplitude = 2.5 V; precharge duration = 4,160 μ s. B, same conditions as A, except the proximal 2 poles of the catheter were disconnected, making the anode equal in size and current density to the cathode.

FIGURE 4. *A*, temporary quadripolar electrode catheter. Pacing stimuli are introduced during the refractory period of sensed beats. Polarization artifact is minimized with a precharge duration of 4,256 μ s. Amplitude = 2.5 V; P = pacing stimulus; S = sensed beat (there is a marker generated by the computer through each sensed beat). *B*, at a pacing amplitude of 1.0 V, the same precharge duration (4,256 μ s) minimizes polarization artifact. *C*, pacing is instituted at a cycle length of 402 ms. At the cathodic threshold, 0.7 V, a large amplitude-evoked potential is generated. Precharge = 4,256 μ s. *D*, pacing amplitude is increased stepwise from 0.7 to 1.0 V across this strip. Although capture is present on every beat, the evoked potential diminishes in size as amplitude increases. Cycle length = 402 ms; precharge = 4,256 μ s. *E*, automatic threshold test failed at 2.5 V because of small signal size that was interpreted as noncapture. Cycle length = 402 ms; precharge = 4,256 μ s.



of an algorithm in which pacing amplitudes are varied automatically and the resultant signals analyzed for capture, noncapture or fusion. At lower pacing amplitudes, once the "template" for capture has been defined by the system, this differentiation should be straightforward. However, at higher pacing amplitudes, the reduction of signal size as we have seen in this study could be misinterpreted as loss of capture, causing a large increase in pacing amplitude to be delivered by the pacemaker because of a falsely determined "increase" in

pacing threshold. High output pacing would thus result, negating the advantages of automatic threshold tracking, which would potentially save generator life by pacing only enough above the true pacing threshold to maintain capture. From the results of this study, we believe that automatic threshold tracking can be accomplished reliably up to stimulus amplitudes of 3 V, but it would not be valid at outputs much above that. Fortunately, threshold tracking above 3 V is not necessary. If the threshold were greater than 3 V, the stimulus ampli-

tude should be at maximum. Alternatively, unipolar sensing should eliminate this phenomenon.

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Effect of Quinidine or Procainamide Versus No Antiarrhythmic Drug on Sudden Cardiac Death, Total Cardiac Death, and Total Death in Elderly Patients with Heart Disease and Complex Ventricular Arrhythmias

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A prospective study correlated the effect of quinidine or procainamide versus no antiarrhythmic drug on sudden cardiac death, total cardiac death and total death in 406 elderly patients with heart disease and asymptomatic complex ventricular arrhythmias detected by 24-hour ambulatory electrocardiograms. Of 397 patients treated with quinidine, 184 (46%) developed adverse effects during the first 2 weeks of therapy and were given no further antiarrhythmic therapy. Of 9 patients treated with procainamide, 2 (22%) developed adverse effects during the first 2 weeks of therapy and were given no further antiarrhythmic therapy. Adverse effects developed during long-term therapy in 6 patients (2%) receiving quinidine and in 3 patients (33%) receiving procainamide. Mean follow-up was 24 ± 15 months in both groups. Sudden cardiac death, total cardiac death and total death occurred in 21, 43 and 65% of patients receiving quinidine or procainamide, respectively, and in 23, 44 and 63% of patients receiving no antiarrhythmic drug, respectively (difference not significant). Survival by Kaplan-Meier analysis showed no significant difference between the 2 groups for sudden cardiac death, total cardiac death or total death through 4 years. Patients with abnormal left ventricular ejection fraction had a 3.4 times higher incidence of sudden cardiac death, a 2.4 times higher incidence of total cardiac death and a 1.4 times higher incidence of total death than patients with normal left ventricular ejection fraction. These data showed no significant difference in sudden cardiac death, total cardiac death or total death between patients treated with quinidine or procainamide or with no antiarrhythmic therapy. The presence or absence of

antiarrhythmic therapy did not affect the event risk regardless of left ventricular ejection fraction $\geq 50\%$ versus $< 50\%$, presence versus absence of VT, or ischemic versus nonischemic heart disease. (Am J Cardiol 1990;66:423-428)

Patients with abnormal left ventricular ejection fraction, with paroxysmal ventricular tachycardia (VT) or with complex ventricular arrhythmias associated with heart disease are at increased risk for new cardiac events.¹⁻¹⁰ VT and complex ventricular arrhythmias associated with heart disease are independent risk factors for death, the mortality rate being highest in patients with both abnormal left ventricular ejection fraction and VT or complex ventricular arrhythmias.¹⁻¹⁰ However, there are no hard data from prospective, randomized, double-blind clinical trials demonstrating that abolition or reduction of VT or complex ventricular arrhythmias by antiarrhythmic drugs will reduce cardiac events or mortality.¹¹ In addition, the available antiarrhythmic drugs may fail to abolish or decrease VT or complex ventricular arrhythmias in the individual patient, may occasionally exacerbate ventricular arrhythmias and may produce toxic effects.¹¹ In the present report, we present the results from a prospective study correlating the effect of quinidine or procainamide versus no antiarrhythmic drug on the incidences of sudden cardiac death, total cardiac death and total mortality in 406 patients with heart disease, older than 62 years, with complex ventricular arrhythmias and no sustained VT detected by 24-hour ambulatory electrocardiograms.

METHODS

In a prospective study, asymptomatic complex ventricular arrhythmias without sustained VT detected by 24-hour ambulatory electrocardiograms were found in 406 patients (nonsustained VT in 81 patients) with heart disease and technically adequate M-mode and 2-dimensional echocardiograms for measuring left ventricular ejection fraction in a long-term health care facility.

Patients with sustained VT were not included in this study. None of the 406 patients was receiving any anti-

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arrhythmic drug at the time of the 24-hour ambulatory electrocardiograms. The 406 patients included 265 women and 141 men, mean age 82 ± 7 years (range 62 to 100). M-mode and 2-dimensional echocardiograms were obtained as previously reported.⁸ M-mode echocardiographic measurements were obtained along the true minor axis of the left ventricle, as confirmed by the 2-dimensional image. If an M-mode tracing could not be obtained along the true minor axis, measurements were made directly from the 2-dimensional study. The long-axis view was used and checked with a cross-sectional view. Measurements were made from a 2-dimensional study in 49% of the subjects. The formula¹² to determine left ventricular volumes at end-diastole and end-systole was as follows: $V = (7.0/2.4 + D)D^3$, where V = volume at end diastole or end-systole and D = the echocardiographically measured left ventricular internal dimension at end-diastole or end-systole. In selected patients with segmental wall motion abnormalities, left ventricular volumes at end-diastole and end-systole were calculated by planimetry from the 2-dimensional study. The left ventricular ejection fraction was calculated as (left ventricular end-diastolic volume - left ventricular end-systolic volume)/left ventricular end-diastolic volume $\times 100\%$. A left ventricular ejection fraction $<50\%$ was considered abnormal.^{5,8}

Ambulatory electrocardiographic monitoring was performed for 24 hours using portable Avionics model 445 tape recorders to obtain 2 leads corresponding to a modified V_1 and V_5 . Tapes were analyzed by a Cardio-Data MK 3 computer system. All rhythm disturbances were written out on electrocardiographic paper at 25 mm/s and verified by 2 cardiologists. VT was defined as at least 3 consecutive ventricular premature complexes.^{1,3,6,8-10,13} Complex ventricular arrhythmias included VT or paired, multifocal or frequent ($\geq 30/\text{hour}$) ventricular premature complexes.⁸⁻¹⁰

Of the 406 patients, 397 (98%) were initially treated with quinidine with an initial dose of 200 mg 4 times daily. Nine patients with a history of intolerance to quinidine were initially treated with procainamide 500 mg 3 to 4 times daily. Quinidine and procainamide blood levels were obtained during initiation of therapy and every 3 months during long-term therapy to maintain a quinidine blood level from 2 to 5 mg/liter and a procainamide blood level from 4 to 10 mg/liter. If during the first 2 weeks of therapy the patients developed adverse symptoms attributable to drug (186 patients), the drug was stopped and no further antiarrhythmic drug administered. These 186 patients formed the no antiarrhythmic therapy group. If the patients developed adverse effects from drug during long-term therapy (9 patients), the drug was stopped and no further antiarrhythmic drug given. These patients were included in the drug treatment group with follow-up ending at the time of drug cessation.

Patients were followed for incidences of sudden cardiac death, total cardiac death and total death. Mean follow-up was 24 ± 15 months (range 1 to 54). Sudden cardiac death was defined as an unexpected cardiac death in a patient with heart disease found dead within

TABLE I Incidence of Adverse Effects from Quinidine or Procainamide in Elderly Patients

	Quinidine (n = 397)		Procainamide (n = 9)	
	No.	%	No.	%
Incidence within 2 weeks of therapy	184	46	2	22
Incidence during long-term therapy	6*	2	3†	33
Total incidence	190	48	5	55

* Including thrombocytopenia in 2 patients; † systemic lupus erythematosus-like syndrome.

TABLE II Baseline Characteristics of Patients Treated with Quinidine or Procainamide and with No Antiarrhythmic Drug

	Quinidine or Procainamide (n = 220)	No Anti- arrhythmic Drug (n = 186)	p Value
Age (yrs)	82 ± 7	83 ± 8	NS
M/F (%)	34/66	35/65	NS
Follow-up (mos)	24 ± 15	24 ± 15	NS
Ventricular tachycardia (%)	20	20	NS
Abnormal LVEF (%)	31	32	NS

NS = not significant; LVEF = left ventricular ejection fraction.

TABLE III Incidences of Sudden Cardiac Death, Total Cardiac Death and Total Death in Patients with Ischemic Heart Disease Treated with Quinidine or Procainamide and with No Antiarrhythmic Drug

	Quinidine or Procainamide (n = 132)		No Anti- arrhythmic Drug (n = 105)		p Value
	No.	%	No.	%	
Sudden cardiac death	36	27	34	32	NS
Total cardiac death	81	61	62	59	NS
Total death	96	73	74	70	NS

NS = not significant.

1 hour of being clinically stable.¹⁴ Patients with fatal primary ventricular fibrillation documented by electrocardiogram (14 receiving antiarrhythmic drug and 9 receiving no antiarrhythmic drug) were classified as having sudden cardiac death. Total cardiac death included deaths due to sudden cardiac death, fatal myocardial infarction or congestive heart failure. Total death included deaths due to any cause. Group comparisons were made using the *t* test for independent means and chi-square analysis. Survival analysis was performed using the method of Kaplan-Meier and Cox-Mantel analysis.

RESULTS

Table I lists the incidence of adverse effects causing cessation of quinidine or procainamide during the first 2 weeks of therapy, during long-term therapy and the total incidence of adverse effects. The most common adverse effects from quinidine were anorexia, nausea,

TABLE IV Incidences of Sudden Cardiac Death, Total Cardiac Death and Total Death in Patients with Nonischemic Heart Disease Treated with Quinidine or Procainamide and with No Antiarrhythmic Drug

	Quinidine or Procainamide (n = 88)		No Antiarrhythmic Drug (n = 81)		p Value
	No.	%	No.	%	
Sudden cardiac death	9	10	8	10	NS
Total cardiac death	14	16	20	25	NS
Total death	47	53	43	53	NS

NS = not significant.

TABLE V Incidences of Sudden Cardiac Death, Total Cardiac Death and Total Death in Patients Treated with Quinidine or Procainamide and with No Antiarrhythmic Drug

	Quinidine or Procainamide (n = 220)		No Antiarrhythmic Drug (n = 186)		p Value
	No.	%	No.	%	
Sudden cardiac death	45	21	42	23	NS
Total cardiac death	95	43	82	44	NS
Total death	143	65	117	63	NS

NS = not significant.

TABLE VI Incidences of Sudden Cardiac Death, Total Cardiac Death and Total Death in Elderly Patients With Nonsustained Ventricular Tachycardia and Complex Ventricular Arrhythmias Without Ventricular Tachycardia

	VT (n = 81)		No VT (n = 325)		p Value
	No.	%	No.	%	
Sudden cardiac death	24	30	63	19	<0.05
Total cardiac death	44	54	133	41	<0.05
Total death	53	65	207	64	NS

NS = not significant; VT = ventricular tachycardia.

vomiting, abdominal pain and diarrhea. Other adverse effects from quinidine included rash, headache, fever, vertigo, confusion, tinnitus, disturbed vision and in 2 patients thrombocytopenia. Adverse effects from procainamide included anorexia, nausea, vomiting, abdominal pain, dizziness and in 3 patients a systemic lupus erythematosus-like syndrome with arthralgia, fever and increased titers of antinuclear antibodies. The adverse effects from quinidine or procainamide were reversible.

Table II lists the baseline characteristics of 220 patients treated with quinidine or procainamide and of 186 patients whose antiarrhythmic drug was stopped within 2 weeks of initiation (the no antiarrhythmic drug group). No significant differences were found between the 2 groups. Tables III, IV and V indicate the incidences of sudden cardiac death, total cardiac death and total death in patients with ischemic heart disease (Table III), nonischemic heart disease (110 with hyperten-

TABLE VII Baseline Characteristics of Patients with Abnormal and Normal LVEF

	Abnormal LVEF (n = 128)	Normal LVEF (n = 278)	p Value
Age (yrs)	83 ± 8	82 ± 7	NS
M/F (%)	39/61	33/67	NS
Follow-up (mos)	18 ± 14	27 ± 14	<0.001
Ventricular tachycardia (%)	27	17	<0.02
Antiarrhythmic therapy (%)	54	54	NS

LVEF = left ventricular ejection fraction; NS = not significant.

TABLE VIII Incidences of Sudden Cardiac Death, Total Cardiac Death and Total Death in Elderly Patients with Abnormal and Normal LVEF

	Abnormal LVEF (n = 128)		Normal LVEF (n = 278)		p Value
	No.	%	No.	%	
Sudden cardiac death	53	41	34	12	<0.001
Total cardiac death	93	73	84	30	<0.001
Total death	103	81	157	57	<0.001

LVEF = left ventricular ejection fraction.

TABLE IX Incidences of Sudden Cardiac Death, Total Cardiac Death and Total Death in Patients with Abnormal Left Ventricular Ejection Fraction Treated with Quinidine or Procainamide and Treated with No Antiarrhythmic Drug

	Quinidine or Procainamide (n = 69)		No Antiarrhythmic Drug (n = 59)		p Value
	No.	%	No.	%	
Sudden cardiac death	27	39	26	44	NS
Total cardiac death	50	72	43	73	NS
Total death	56	81	47	80	NS

NS = not significant.

sion, 54 with valvular heart disease and 5 with cardiomyopathy) (Table IV) and in all patients (Table V) treated with quinidine or procainamide and treated with no antiarrhythmic drug. No significant differences were found between the patients treated with quinidine or procainamide and treated with no antiarrhythmic drug.

Table VI lists the incidences of sudden cardiac death, total cardiac death and total death in patients with nonsustained VT and in patients with complex ventricular arrhythmias without VT and levels of statistical significance. The density of ventricular arrhythmias did not predict the occurrence of sudden cardiac death or total cardiac death.

Table VII lists the baseline characteristics of 128 patients with abnormal left ventricular ejection fraction and of 278 patients with normal left ventricular ejection fraction and levels of statistical significance. Table VIII indicates the incidences of sudden cardiac death, total cardiac death and total death in patients with abnormal left ventricular ejection fraction and in patients with normal left ventricular ejection fraction and levels of statistical significance.

TABLE X Incidences of Sudden Cardiac Death, Total Cardiac Death and Total Death in Patients with Ventricular Tachycardia Treated with Quinidine or Procainamide and Treated with No Antiarrhythmic Drug

	Quinidine or Procainamide (n = 43)		No Antiarrhythmic Drug (n = 38)		p Value
	No.	%	No.	%	
Sudden cardiac death	12	28	12	32	NS
Total cardiac death	23	53	21	55	NS
Total death	29	67	24	63	NS

NS = not significant.

TABLE XI Incidences of Sudden Cardiac Death, Total Cardiac Death and Total Death in Patients with Ventricular Tachycardia and with Abnormal Left Ventricular Ejection Fraction Treated with Quinidine or Procainamide and Treated with No Antiarrhythmic Drug

	Quinidine or Procainamide (n = 19)		No Antiarrhythmic Drug (n = 15)		p Value
	No.	%	No.	%	
Sudden cardiac death	9	47	8	53	NS
Total cardiac death	16	84	12	80	NS
Total death	16	84	12	80	NS

NS = not significant.

Tables IX, X and XI list the incidences of sudden cardiac death, total cardiac death and total death in patients with abnormal left ventricular ejection fraction alone (Table IX), VT alone (Table X) and VT with abnormal left ventricular ejection fraction (Table XI) treated with quinidine or procainamide and treated with no antiarrhythmic drug. No significant differences were found between patients treated with quinidine or procainamide and treated with no antiarrhythmic drug. In patients with a left ventricular ejection fraction <40%, no significant differences in sudden cardiac death, total cardiac death and total death were observed between patients treated with quinidine or procainamide and treated with no antiarrhythmic drug.

Kaplan-Meier survival curves for sudden cardiac death (Figure 1), for total cardiac death (Figure 2) and for total death (Figure 3) are shown for patients treated with quinidine or procainamide and for patients treated with no antiarrhythmic drug. Cox-Mantel analysis showed no significant differences between the group treated with quinidine or procainamide compared to the

group treated with no antiarrhythmic drug for sudden cardiac death, total cardiac death or total death. The incidence of syncope or near-syncope was also not significantly reduced by quinidine or procainamide.

A limitation of our study is that follow-up 24-hour ambulatory electrocardiograms were obtained in only 25 of 43 patients (58%) with nonsustained VT while receiving quinidine or procainamide and in only 88 of 220 patients (40%) with complex ventricular arrhythmias while receiving quinidine or procainamide. Follow-up 24-hour ambulatory electrocardiograms showed that nonsustained VT was reduced more than 90% in 21 of 25 patients (84%) receiving quinidine or procainamide and not significantly affected in the other 4 patients (16%). The average number of ventricular premature complexes/hour was reduced more than 70% in 72 of 88 patients (82%) receiving quinidine or procainamide and not significantly affected in the other 16 patients (18%). No significant differences in sudden cardiac death, total cardiac death or total death were observed

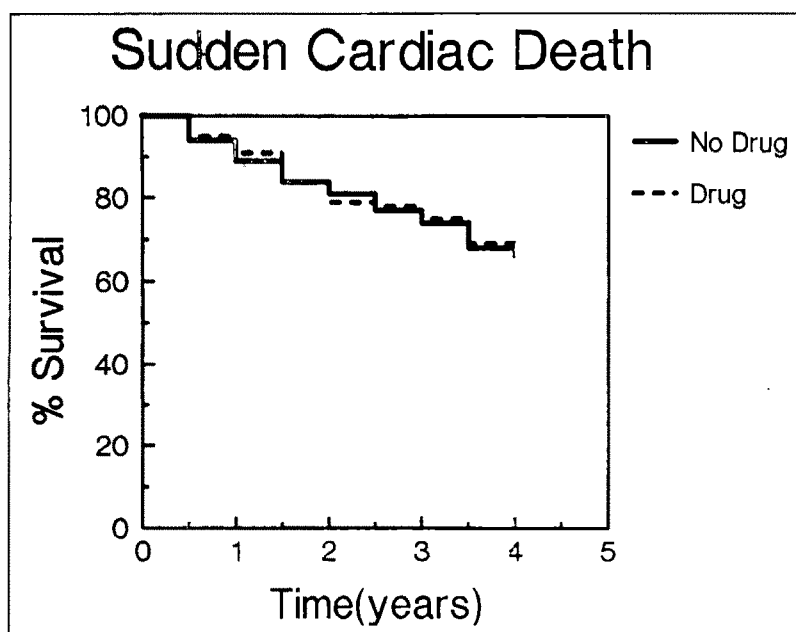


FIGURE 1. Kaplan-Meier survival curves for sudden cardiac death in patients treated with no antiarrhythmic drug (I) and in patients treated with quinidine or procainamide (II). Number of patients in each time interval as shown in Figure III.

between patients who had satisfactory or unsatisfactory suppression of their complex ventricular arrhythmias by quinidine or procainamide.

DISCUSSION

Many studies have shown that the mortality rate is highest in patients with both abnormal left ventricular ejection fraction and VT or complex ventricular arrhythmias.¹⁻¹⁰ Data from this study in elderly patients with heart disease and asymptomatic complex ventricular arrhythmias showed in patients with abnormal left ventricular ejection fraction a 3.4 times higher incidence

of sudden cardiac death, a 2.4 times higher incidence of total cardiac death and a 1.4 times higher incidence of total death than in patients with normal left ventricular ejection fraction.

Patients with complex ventricular arrhythmias and no heart disease have a good prognosis^{8,15-17} and should not be treated with antiarrhythmic drugs. Although patients with VT or complex ventricular arrhythmias associated with heart disease are at increased risk for new cardiac events,¹⁻¹⁰ there are no hard data showing that abolition or reduction of VT or complex ventricular arrhythmias by antiarrhythmic drugs will decrease car-

FIGURE 2. Kaplan-Meier survival curves for total cardiac death in patients treated with no antiarrhythmic drug (I) and in patients treated with quinidine or procainamide (II). Number of patients in each time interval as shown in Figure III.

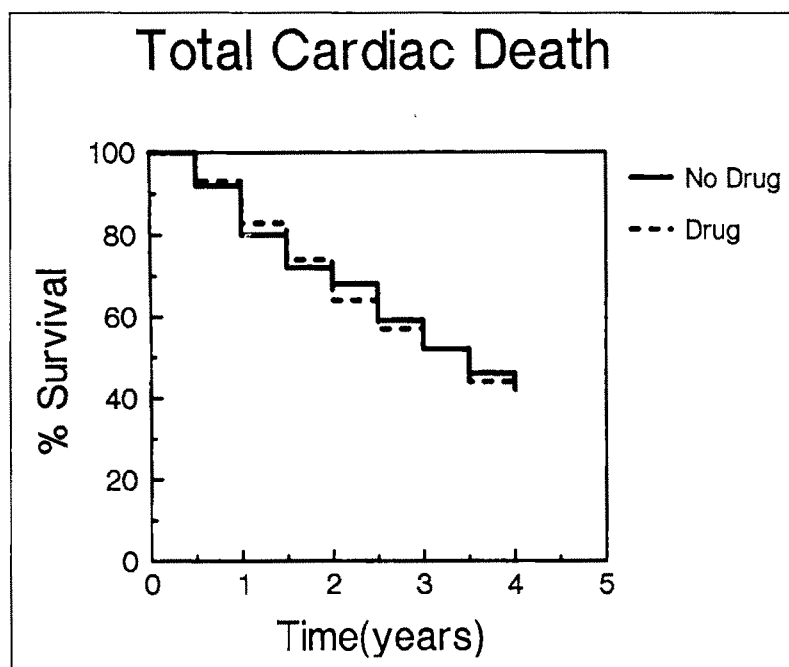
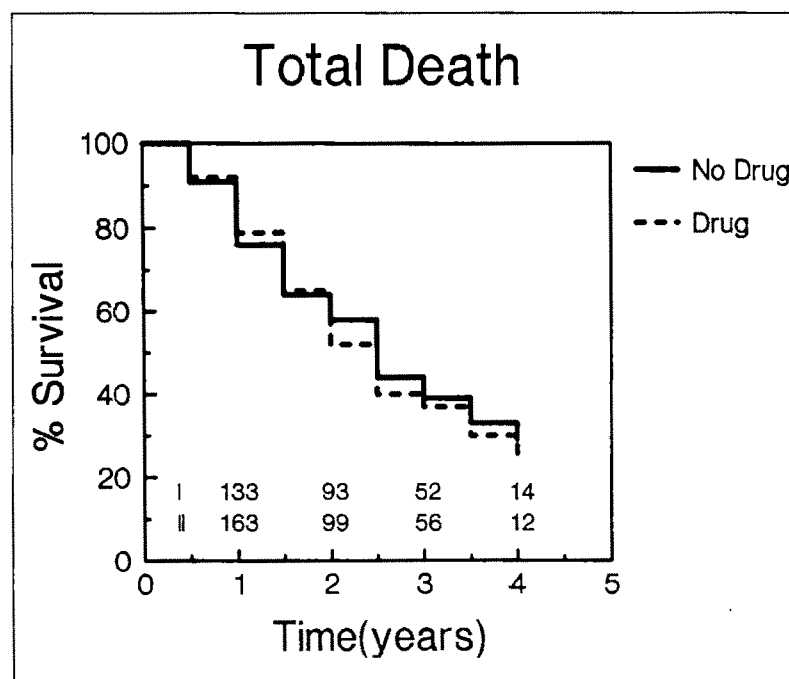


FIGURE 3. Kaplan-Meier survival curves for total death in patients treated with no antiarrhythmic drug (I) and in patients treated with quinidine or procainamide (II). Numbers refer to number of patients in each time interval.



diac events or mortality.¹¹ Late proarrhythmic effects may also occur during long-term antiarrhythmic therapy.¹⁸

The Cardiac Arrhythmia Suppression Trial showed that both encainide and flecainide used to treat asymptomatic or mildly symptomatic ventricular arrhythmias after myocardial infarction caused an increase in arrhythmic death, nonfatal cardiac arrest and total mortality in comparison with placebo.¹⁹ This study is still evaluating the use of moricizine.¹⁹ No significant difference in mortality was observed in postinfarction patients treated with procainamide,²⁰ tocainide,^{21,22} mexiletine,^{23,24} phenytoin^{25,26} and aprindine²⁷ in comparison with placebo.

Data from our study showed that elderly patients developed a high incidence of adverse effects from quinidine (48%) or procainamide (55%) causing cessation of therapy. Quinidine or procainamide did not cause any reduction in sudden cardiac death, total cardiac death or total death in comparison with no antiarrhythmic therapy in our patients with heart disease and complex ventricular arrhythmias with normal or abnormal left ventricular ejection fraction. These data raise the question of whether antiarrhythmic drugs should be administered to elderly patients with heart disease and asymptomatic or mildly symptomatic ventricular arrhythmias that are not life-threatening.

Finally, our data do not apply to patients with life-threatening ventricular arrhythmias. Tresch et al²⁸ have shown that antiarrhythmic drugs or cardiac surgery (including automatic defibrillator insertion), or both, may be indicated in elderly patients with refractory symptomatic ventricular tachycardia and ventricular fibrillation. However, our data show no benefit of antiarrhythmic therapy in most patients with complex ventricular arrhythmias for whom antiarrhythmic therapy is administered.

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Congestive Heart Failure: Current Controversies and Future Prospects

Barry M. Massie, MD, and Milton Packer, MD

Each of the last 3 decades has been witness to a major advance in our understanding of the pathophysiology and treatment of congestive heart failure. In the 1960s, potent new diuretics revolutionized the management of the edematous patient. In the 1970s, the concept of vasodilator therapy was first introduced, although it was initially applied with success only to intravenous agents. In the 1980s, the orally active converting-enzyme inhibitors were first administered to patients with chronic heart failure and gained widespread acceptance after controlled studies showed that these drugs not only improved symptoms, but prolonged life. What challenges remain for the clinician as we enter the 1990s?

The challenges are indeed enormous. Despite the advances of the past 30 years, congestive heart failure is a major cause of morbidity and mortality. Heart failure afflicts nearly 4 million patients in the United States and causes nearly 400,000 deaths each year. It is the only cardiovascular disorder that is increasing in prevalence and constitutes the most common cause for hospitalization to medical services in patients >65 years old. Despite the use of digitalis, diuretics and the converting-enzyme inhibitors, most patients with congestive heart failure are destined to suffer considerable disability and die from their disease. These epidemiologic observations lead to the following conclusion: heart failure remains a major public health problem and an important area for laboratory and clinical research.

The following articles summarize the proceedings of the meeting, "Congestive Heart Failure: Current Controversies and Future Prospects," which was attended by over 1,200 physicians and was held in Jerusalem in conjunction with the First International Symposium on Heart Failure in May 1989. The intent of this program was to highlight the most important unresolved issues in the field of heart failure and to speculate about future developments, both from the perspective of the clinician as well as the investigator in basic research. Some of the key controversies in heart failure for the 1990s were presented in debate format, primarily as a didactic tool. This approach permitted the audience to listen to both sides of each question, but required the debaters to present polarized (and often extreme) arguments, which meant that they had to occasionally adopt positions that they might not assume in their usual practice. The truth and the optimal management of individual patients nec-

essarily lies between the 2 extreme positions taken on each question.

The first debate concerns the appropriate management of ventricular arrhythmias in patients with chronic heart failure. Nearly all patients with this disease have frequent and complex ventricular ectopic beats and experience nonsustained episodes of ventricular tachycardia; the latter carries a particularly unfavorable prognosis. Should these ventricular arrhythmias, if asymptomatic, be treated to prevent the subsequent occurrence of sudden death? Drs. Anderson and Podrid discuss the advantages and disadvantages of antiarrhythmic drug therapy in patients with severely impaired ventricular function. The question of using antiarrhythmic drugs has been the focus of intense debate since the publication of the results of the Cardiac Arrhythmia Suppression Trial (CAST); the papers highlight the soul searching experienced by all physicians who treat patients with heart failure in the postCAST era.

The second debate focuses on the usefulness of direct-acting vasodilators in the treatment of heart failure. The most commonly used representatives of this class are the organic nitrates, which were the first vasodilators used for the long-term treatment of chronic heart failure over a decade ago. At that time, their use was not seriously questioned by the cardiology community. However, doubts about their role have recently surfaced with reports of the nearly universal development of nitrate tolerance; such doubts have received particular attention in the era marked by the increasing acceptance of the use of converting-enzyme inhibitors. Can nitrates still be considered effective agents in the treatment of heart failure? Drs. Cohn and Packer discuss this question and try to resolve the discordant results of available studies.

The final debate centers on the role of converting-enzyme inhibitors in patients with early or mild heart failure. The articles that follow show that the field is in a time of transition from present management practices to potential future strategies. Should all patients with left ventricular systolic dysfunction be treated with a converting-enzyme inhibitor? While the benefit of this approach cannot be determined from the available data, physicians must often deal with the question of whether an effective treatment in the advanced stages of a disease may have a role if administered earlier. Dr. Massie suggests that these drugs may prevent progression of the disease, whereas Dr. Rahimtoola argues that the facts do not presently support this approach.

Finally, 2 perspectives focus on possible future directions in heart failure, setting the stage for additional controversies in the next decade. Dr. Poole-Wilson presents the view of the clinician, summarizing the poten-

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tial changes that are likely to occur in the practical management of this disorder. Dr. Katz, on the other hand, views the future from the perspective of the basic scientist, suggesting that the burgeoning knowledge of myocardial biochemistry and cellular and molecular biology will have an important impact on both our understanding and treatment of heart failure.

This series of articles would not have been possible without the support and assistance of many individuals. We congratulate Drs. Asher Kimchi and Basil Lewis,

who (almost singlehandedly) organized the highly successful Jerusalem meeting. We are grateful to Squibb International, which supported the original presentation of these papers in Jerusalem. Initially, it was not our intent to publish these papers. It was only after the enthusiastic response to the meeting and the encouragement of Dr. William C. Roberts that we became excited about preparing these manuscripts for publication and are pleased to see them presented in *The American Journal of Cardiology*.

Effect of Milrinone on Ventricular Arrhythmias in Congestive Heart Failure

Kevin J. Ferrick, MD, Steven A. Fein, MD, Aileen M. Ferrick, RN, and Joseph T. Doyle, MD

Milrinone is a nonglycoside, noncatecholamine inotropic agent that has been shown to exhibit inotropic and vasodilatory effects in patients with severe congestive heart failure (CHF).¹⁻⁴ It is a bipyridine analog of amrinone that has been shown in experimental studies to be significantly more potent than the parent compound on a per weight basis. Although its mechanism of action has not been fully defined, it has been suggested that enhancement of calcium ion fluxes in the myocardial cell is contributory.⁵ Heart failure secondary to verapamil or propranolol can be improved with milrinone and its inotropic effect can be detected despite concomitant therapy with either catecholamine or glycoside agents. The effect of milrinone on ventricular arrhythmias has not been completely defined. Several studies have suggested that ventricular arrhythmias can be exacerbated in some patients treated with either amrinone⁶ or milrinone.⁷⁻⁹ Ventricular arrhythmias, including complex features such as non-sustained ventricular tachycardia (VT), are common in patients with CHF and have been implicated in the high mortality of the disease.¹⁰ We attempted to determine if chronic treatment with milrinone affects the prevalence and complexity of ventricular arrhythmias in patients with CHF.

METHODS

Patient selection: The study population consisted of 29 patients enrolled at our institution as part of a multicenter trial investigating the hemodynamic effects of milrinone administration. Entry criteria for the study included New York Heart Association class II to IV CHF that had been stable for ≥ 2 weeks, left ventricular ejection fraction $< 40\%$, age ≥ 18 years and either a cardiac index of ≤ 2.5 l/min/m² or a pulmonary artery wedge pressure ≥ 15 mm Hg. Patients were excluded from enrollment for any of the following reasons: myocardial infarction within 3 months; unstable angina; CHF secondary to valvular disease; renal insufficiency (creatinine ≥ 3 mg/dl); primary pulmonary or hepatic dysfunction; or a history of sustained VT or ventricular fibrillation. Self-terminating VT > 6 complexes in duration on an initial 24-hour ambulatory electrocardiographic recording was an additional exclusion criterion.

The 24 patients who underwent quantitative 24-hour ambulatory electrocardiographic recording at baseline and after initiation of milrinone therapy during either no or unchanged antiarrhythmic therapy are the subjects of this report.

Patient characteristics: The patient population consisted of 24 patients on either no or unaltered antiarrhythmic therapy; 19 were men. Patients were not excluded on the basis of arrhythmia frequency. The group had a mean age of 61 years (range 41 to 80). Heart failure was secondary to coronary artery disease in 17 patients and idiopathic dilated cardiomyopathy in 7 patients. All patients had severe left ventricular dysfunction with a mean ejection fraction for the group of 0.21 (range 0.12 to 39).

Arrhythmia analysis: Patients underwent quantitative 24-hour ambulatory electrocardiographic recording both before milrinone therapy and after initiation of a stable oral milrinone dose. Follow-up ambulatory electrocardiographic recordings were performed 5 to 21 days (mean 8.6) after initiation of milrinone therapy; 15 patients were on no antiarrhythmic agents during either the control or follow-up 24-hour ambulatory electrocardiogram. The 9 patients who were taking antiarrhythmic agents during the premilrinone ambulatory recording were continued on the same maintenance dose during the follow-up Holter recording. Recordings were scanned using a software-based user-interactive system either at our institution (Marquette 8000 system) or at an independent scanning service (Clinical Data). Recordings were quantitatively analyzed for total density of ventricular premature complexes (VPCs), number of ventricular couplets and number of runs of VT and total repetitive ectopy (number of couplets plus number of runs).

Proarrhythmic criteria: Proarrhythmic responses were judged by the criteria of Velebit¹¹ and Morganroth.¹² Velebit has proposed that any of the following responses constitutes a proarrhythmic effect: a ≥ 4 -fold increase in total VPC density; a ≥ 10 -fold increase in the frequency of repetitive events (couplets and runs of nonsustained VT); and the occurrence of not previously documented sustained VT. In an attempt to account for spontaneous variability in VPC density, Morganroth has suggested that the criteria by which proarrhythmia is judged should be a function of baseline arrhythmia frequency. Specifically, the following responses have been suggested: a ≥ 10 -fold increase in VPC density if the baseline frequency of ectopy is between 1 to 50 VPCs per hour; a ≥ 5 -fold increase for baseline VPC densities of 51 to 100 VPCs per hour; a ≥ 4 -fold increase for baseline VPC densities of 101 to 300 VPCs per hour; and a ≥ 3 -fold increase in overall VPC density

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TABLE I Definitions of Pro- and Antiarrhythmic Effect

Proarrhythmic Effect	
Velebit	
4-fold increase in hourly VPC frequency	
10-fold increase in hourly frequency of repetitive forms (couplets or VT)	
First occurrence of sustained VT (>60 s)	
Morganroth	
Presence of a new ventricular tachyarrhythmia not related to other factors	
Change in a previously documented ventricular arrhythmia	
Increased VPC frequency	
Mean Hourly VPC Frequency at Baseline	Increase Required for Proarrhythmia
1 to 50	10X
51 to 100	5X
101 to 300	4X
≥301	3X
Marked increase in rate of VT	
Change in type of ventricular tachyarrhythmia, such as nonsustained VT to sustained VT, sustained VT to torsades de pointes or VT to ventricular fibrillation	
Marked change in ease of termination of ventricular tachyarrhythmia	
Antiarrhythmic effect (Podrid)	
50% decrease of VPC frequency	
+	
90% decrease of couplets	
+	
Abolition of ventricular tachycardia	
VPC = ventricular premature complex; VT = ventricular tachycardia.	

for baseline ectopy of >300 VPCs per hour. Additional criteria include a marked increase in rate of VT or a change in the type of ventricular tachyarrhythmia such as conversion of nonsustained VT to sustained VT or sustained VT to torsades de pointes (Table I).

Antiarrhythmic criteria: Criteria as defined by Podrid¹³ were used to assess any antiarrhythmic effect of milrinone administration. Specifically, a 50% decrease in total VPC density in concert with a 90% decrease of ventricular couplets and total abolition of VT was felt to represent an antiarrhythmic effect (Table I).

Statistical analysis: Values are expressed as mean \pm standard deviation. Analysis of arrhythmia data was performed using the Wilcoxon test for nonparametric paired data. A *p* value ≤ 0.05 was considered statistically significant.

Study protocol All patients underwent an initial screening consisting of a complete history and physical examination, laboratory examinations including complete blood count, serum chemistries, chest x-ray, resting radionuclide left ventriculography and a 24-hour quantitative baseline ambulatory electrocardiographic recording. Patients meeting all eligibility requirements were subsequently admitted to the hospital for hemodynamic monitoring during initiation of milrinone therapy. The patient's milrinone dose was titrated according to initial clinical and hemodynamic response and patients were discharged to outpatient follow-up on an average milrinone dosage of 7.5 mg (range 7.5 to 10) every 6 hours. A follow-up 24-hour ambulatory electro-

cardiographic recording was obtained 5 to 21 days (mean 8.6) after milrinone therapy was begun.

RESULTS

The arithmetic mean VPC density (\pm standard deviation) for the group before milrinone administration was $5,222 \pm 5,328$ VPCs/24 hours. All patients manifested ventricular ectopic activity. In 17 of the 24 patients, >100 VPCs per hour on average were noted. Ventricular couplets were seen in 23 patients with 10 of them exhibiting >10 couplets per hour. VT was seen in 20 patients and 9 of them exhibited >10 episodes of VT. All episodes were self-terminating. Milrinone administration did not affect the proportion of patients exhibiting VPCs, ventricular couplets and VT. During oral milrinone therapy, the mean total VPC frequency increased to $8,632 \pm 8,670$ (*p* < 0.05). The frequency of ventricular couplets increased from a mean of $290 \pm 425/24$ hours before milrinone therapy to $907 \pm 1,193$ (*p* < 0.01) during milrinone therapy. Similarly, the frequency of episodes of VT increased from a baseline mean of $13 \pm 20/24$ hours to 130 ± 267 (*p* < 0.05). Total repetitive forms defined as frequency of ventricular couplets plus episodes of VT increased from a mean of $303 \pm 435/24$ hours to $1,037 \pm 1,398$ (*p* < 0.01) during milrinone therapy (Table II).

When specific proarrhythmic criteria were applied to individual patients, 8 met proarrhythmic criteria as described by Velebit and 7 met the criteria outlined by Morganroth et al.¹² Of the patients satisfying Velebit criteria, 6 met criteria on the basis of total VPC frequency and 7 met criteria on the basis of increase seen in repetitive ectopy. Both criteria were satisfied by 5 patients. Of the 7 patients meeting Morganroth criteria, all were on the basis of increase in total VPC frequency; 1 patient also met criteria defined by a marked increase in the rate of VT. No patient showed conversion of self-terminating VT to sustained VT or sustained VT to torsades de pointes.

A single patient met Podrid¹³ criteria for antiarrhythmic effect, showing a 90% decrease in VPC frequency and a 100% decrease of repetitive ventricular ectopy.

When left ventricular ejection fraction was compared in patients with and without a proarrhythmic effect, no significant difference was seen between the 2 groups. Specifically, in the 8 patients satisfying proarrhythmic criteria, the mean left ventricular ejection fraction was 0.20 with a range of 0.10 to 0.26. The mean left ventricular ejection fraction in the 16 patients without evidence of proarrhythmic effect was 0.22 with a range of 0.12 to 0.39.

In response to an arrhythmia exacerbation identified at the time of the follow-up, patients either had their milrinone dose altered or were begun on antiarrhythmic therapy. The effect on survival of a proarrhythmic response was therefore not prospectively studied. Nevertheless, all patients meeting either Velebit or Morganroth criteria for proarrhythmia died 41 to 750 days (mean 262) after initial enrollment. Sudden death oc-

TABLE II Effect of Milrinone on Mean Ventricular Ectopic Activity

	Ventricular Ectopy (mean/24 hours \pm SD)			
	Total Frequency	Couplets	VT	Repetitives
Before milrinone	5,222 \pm 5,328	290 \pm 425	13 \pm 20	303 \pm 435
During milrinone	8,632 \pm 8,670*	907 \pm 1,193†	130 \pm 267†	1,037 \pm 1,398†

* $p < 0.05$; † $p < 0.01$ compared with premilrinone.
SD = standard deviation; VT = ventricular tachycardia.

curred in 4 of these patients. Of the remaining 16 patients who did not show a proarrhythmic response, 13 died a mean of 166 days after enrollment. Sudden death occurred in 6 of these patients. No patient presented with documented sustained VT.

DISCUSSION

The recognition that cardioactive medications can have an adverse effect on cardiac conduction and cardiac arrhythmias is not new. As early as 1785, William Withering¹⁴ described several clinical vignettes acknowledging the potential adverse effects of therapy with digitalis. Newer cardiotonic agents have also been shown to exert an effect on cardiac arrhythmias. Amrinone has previously been shown to affect cardiac conduction in an animal model.^{15,16} A subsequent study by Packer⁶ reported that 4 of 31 patients with CHF treated with amrinone developed sustained VT and that the mortality rate for the treated group was higher than historic control subjects. Milrinone, another nonglycoside, noncatecholamine inotropic agent, has also been reported to affect conduction and automaticity in canine Purkinje fibers.¹⁷

In this investigation, we studied the effect of milrinone on the frequency of ventricular ectopic activity in patients with severe CHF. By applying previously reported, standardized definitions of proarrhythmia, we attempted to determine the frequency of proarrhythmia in patients treated with milrinone. Several reports have attempted to address this issue. Holmes et al⁷ reported that 7 of 20 patients with severe CHF treated with milrinone showed more frequent or complex ventricular arrhythmias while taking milrinone. The criteria used in this study to assess "arrhythmia deterioration" were different from either Morganroth or Velebit definitions for proarrhythmia. In the Holmes' study, >10-fold increase in VPC frequency or a >10-fold increase in any complex form (couplets or salvos) was felt to represent arrhythmia deterioration. The occurrence of >5 episodes of any complex form (couplets, salvos, runs of VT) was also considered arrhythmia deterioration. Of note, although 7 of 20 patients met these criteria, there was no significant change in VPC density for the group as a whole during milrinone therapy. One patient showed improvement in arrhythmia frequency. Anderson et al¹⁸ studied 12 patients with 24-hour ambulatory electrocardiographic monitoring during a constant infusion of intravenous milrinone in patients with congestive heart failure. Two patients met Velebit criteria for proar-

rhythmia and a trend toward an increased frequency of VPCs was noted as well as an increase in the number of ventricular couplets and runs of VT. These data correlate well with those of our study in which assessment of arrhythmia frequency was obtained during steady-state therapy with oral milrinone as opposed to intravenous therapy.

The results of a randomized trial comparing milrinone, digoxin and combination therapy in patients with moderately severe CHF has recently been reported by DiBianco et al.¹⁸ This study, involving 230 patients randomized to treatment with either milrinone, digoxin, milrinone plus digoxin or placebo, showed improved exercise tolerance and a decreased frequency of worsening CHF in patients treated with milrinone. Arrhythmia aggravation as defined by Morganroth was seen in 18% of patients treated with milrinone either alone or in combination with digoxin. Arrhythmia aggravation using Velebit criteria was not assessed. A trend toward an increased frequency of ventricular couplets was noted in the milrinone-treated group. Although the DiBianco study does not report if either the frequency of total ventricular ectopy or frequency of VT increased after treatment; the trend toward an increase in ventricular couplets is supported by our study. Moreover, the percentage of patients meeting Morganroth's definition for proarrhythmia is similar to that of this study (29 vs 18%).

This study was not designed as a survival trial and in view of the small number of patients studied and the variable therapeutic response to arrhythmia exacerbation, the mortality data are difficult to interpret. It is likely that the high mortality for the group as a whole can be attributed to the severity of CHF and left ventricular dysfunction in the patients studied.

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Vasodilators Have Not Been Shown to Be of Value in All Patients with Chronic Congestive Heart Failure due to Left Ventricular Systolic Dysfunction

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Vasodilating agents are valuable pharmacologic adjuncts in the management of patients with congestive heart failure (CHF).¹ Recent data suggesting decreased mortality with the use of these agents (see later) has led to the recommendation by some that vasodilators should be used in all symptomatic patients with CHF.² It is important, however, to carefully scrutinize the available data in order to avoid reaching conclusions not wholly supported by this data. First, most patients in reported series often have long-standing, resistant CHF and may not reflect patients seen in routine clinical practice. Many of the reported series also contain patients with varying degrees of severity of CHF; whether CHF is classified by subjective clinical parameters or objective exercise criteria, the results of clinical trials should only be extrapolated to patients who would meet entry criteria for such trials.

In this discussion, we will examine the available data from recent clinical trials and use this data to place the role of vasodilator therapy for patients with CHF in proper clinical perspective. It will become apparent that the available data does not support the routine administration of vasodilators to all patients with CHF.

Mortality data: Patients with chronic resistant CHF have a high mortality rate, which is directly related to the degree of severity of symptoms.^{3,4} Any therapy that might favorably impact on this poor survival rate is of major clinical importance. Recently, 2 large clinical trials have addressed the effect of vasodilators on survival in patients with CHF.^{3,5,6}

In the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial,⁵ patients with severe (class IV) resistant CHF while on digitalis, diuretics and, in some cases, other vasodilating drugs, received either enalapril or placebo. In this trial, the mortality decrease observed in the enalapril group provides evidence favoring the administration of angiotensin-converting enzyme (ACE) inhibitors to all patients with class IV CHF.

In the Veterans Administration Heart Failure Trial,^{3,6} patients with resistant class II and III CHF while on digitalis and diuretics were then continued on digitalis and diuretics, with the addition of either isosorbide dinitrate plus hydralazine, prazosin or placebo. No benefit was observed with prazosin and this agent will not be discussed further. While mortality was decreased in the patients receiving the combination of isosorbide dinitrate and hydralazine, these results were only of marginal statistical significance, despite the use of multiple, complex statistical tests.⁶

In the CONSENSUS trial,⁵ as listed in Table I, major decreases in mortality were observed in those patients receiving enalapril only during the first 6 months of therapy, with no additional mortality decrease noted during the second 6 months of treatment. Upon careful review of the data from this trial, it appears that most of the favorable effect of enalapril on survival in fact occurred during the first 3 months of treatment. Similarly, in the Veterans Administration Heart Failure Trial,⁶ the mortality decrease in patients receiving isosorbide dinitrate and hydralazine was most evident only during the first 12 months of therapy (Table I). Thus, these trials do not provide definitive evidence of continued benefit with vasodilator treatment beyond 6 and 12 months, respectively.

Why are the survival benefits observed in the Veterans Administration Heart Failure Trial less impressive than those of the CONSENSUS trial? Most importantly, patients with resistant class II and III CHF have a much lower baseline mortality than patients with resistant class IV symptoms (52% annual mortality in the CONSENSUS trial),⁵ so significant mortality decrease in less ill patients may be more difficult to show. Even within the Veterans Administration Heart Failure Trial group, patients with class III symptoms receiving placebo had a higher annual mortality than those with Class II symptoms (24.5 versus 12.8%); class III patients had a greater decrease in annual mortality with the combination of isosorbide dinitrate and hydralazine (decreased from 24.5 to 19.7%) than did the patients with class II symptoms (decreased from 12.8 to 9.7%).³ Finally, only 55% of patients in the Veterans Administration Heart Failure Trial were able to tolerate the initially prescribed doses of isosorbide dinitrate and hydralazine, which may have blunted the mortality decrease afforded by this combination of vasodilators.⁶

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TABLE I Effects of Vasodilators on Mortality in Patients with Resistant Heart Failure

	Mortality	
	Digitalis + Diuretics (%)	Digitalis + Diuretics + Vasodilators (%)
Enalapril—Class IV ⁵		
0 to 6 months	44	26
6 to 12 months	8	10
0 to 12 months	52	36
ISDN-Hyd—Class II–III ⁶		
0 to 12 months	19.5	12.1
12 to 24 months	14.8	13.5
24 to 36 months	12.6	10.6
36 to 48 months	6.7	13.5
0 to 48 months	53.6	49.7
12 to 48 months	34.1	37.6

ISDN-Hyd = isosorbide dinitrate plus hydralazine.

TABLE II Findings of the Digoxin-Captopril Multicenter Study¹⁶

No significant differences between digoxin and captopril groups for increase in exercise duration ($p < 0.10$)
Significant increase in left ventricular ejection fraction only in digoxin group ($p < 0.05$)
Fewer withdrawals from study due to treatment failures in digoxin group versus captopril group (4.2 vs 5.8%, $p < 0.05$)
Significant reduction in frequent premature ventricular beats only in captopril group ($p < 0.05$)
Fewer adverse drug reactions in digoxin group versus captopril group (30.2 vs 44.2%)
No difference between digoxin and captopril groups in mortality, hospitalizations or emergency room visits

Thus, available data shows benefit of adding vasodilators to digitalis and diuretic therapy, at least for 6 to 12 months in patients with class IV and III chronic CHF. In the class II patient, there is no randomized trial showing improved survival with vasodilators; therefore, the decision to use vasodilator therapy in these patients must be based upon evidence other than survival benefit.

Exercise capacity/left ventricular function data: In patients with class II CHF, demonstration of improvement in exercise capacity, hemodynamics and left ventricular function may be a more practical endpoint than attempting to further decrease a relatively low mortality rate. Improving exercise capacity is desirable in patients with chronic CHF; such improvement has been convincingly shown both with ACE inhibitors^{7–9} and with digitalis.^{10–15} Two recent trials have directly compared the relative effect of these 2 classes of agents on exercise capacity in patients with CHF. The first such trial compared regimens of diuretics alone, diuretics plus digoxin and diuretics plus captopril in patients with predominantly class II CHF and was recently reported by The Captopril-Digoxin Multicenter Research Group.¹⁶ This study showed increased exercise duration in both the digoxin and captopril groups, with no significant difference between the 2 for the degree of increased duration (when analyzed according to “intention to treat”). Left ventricular ejection fraction in this study was increased

TABLE III Clinical Aspects of Vasodilator Therapy in Heart Failure

Significant incidence of poor response to therapy ^{23,24,28}
Significant incidence of side effects and adverse drug reactions ^{6,17,24,29}
Potential negative inotropic properties of converting enzyme inhibitors ¹⁹
Require multiple daily doses, with possible adverse effects on patient compliance ²⁶
Higher cost to patient

TABLE IV Recommendations for Pharmacologic Therapy of Heart Failure—1990

Functional class IV
Digitalis + diuretics + angiotensin-converting enzyme inhibitor
Additional therapy as needed
Functional class III
Digitalis + diuretics + angiotensin-converting enzyme inhibitor
Additional therapy as needed
Functional class II
Digitalis + diuretics
Angiotensin-converting enzyme inhibitor if signs and symptoms not controlled
Additional therapy as needed
Functional class I
Insufficient data to recommend specific therapy

only in the group receiving digoxin. These and other conclusions from this important study are listed in Table II.

The findings of the Digoxin-Captopril Multicenter Study¹⁶ must be further placed in the perspective of some potential bias inherent in the study design and randomization process. Sources of this potential bias included the following: patients receiving digoxin were older than those receiving captopril (58.2 vs 54.5 years, $p < 0.02$); the digoxin group contained a higher number of patients with class III symptoms than the captopril group (20 versus 9%); patients were only entered in the study if they could tolerate initial “test” doses of captopril (potential bias in favor of captopril); 30 patients were not included in the study due to worsening symptoms during initial withdrawal of digitalis (most patients had been on chronic digitalis therapy); patients excluded from the study due to deterioration after digitalis withdrawal could potentially have excluded those likely to benefit the most from digitalis; and serum digoxin levels were adjusted to a trough level ≤ 2.4 ng/ml, a level that might have resulted in an increased risk of toxic effects. Despite these potential sources of bias, the conclusions of this study listed in Table II suggest that digitalis is at least as clinically efficacious, if not more efficacious than captopril in patients with predominantly class II chronic resistant CHF.

The second recent trial comparing digitalis and ACE inhibitors in patients with CHF was reported by The French Multicenter Study Group.¹⁷ This trial evaluated regimens of digoxin plus diuretics and enalapril plus diuretics in patients with predominantly class II and III symptoms. In this study, no significant differences between the digoxin and enalapril groups were observed for either decrease in symptoms or improvement in exercise capacity, although patients receiving digoxin experienced a trend to slightly fewer adverse drug effects

(10% of patients receiving digoxin versus 18% of patients receiving enalapril [difference not significant]).

In addition to improvement in exercise duration and decrease in symptoms, improvement in left ventricular ejection fraction may be a desirable endpoint in patients with CHF. In the Veterans Administration Heart Failure Trial,³ a nearly 2-fold increase in mortality was noted in the placebo-treated patients (digoxin and diuretic group) with an ejection fraction ≤ 0.28 as opposed to those with an ejection fraction > 0.28 (25.1 vs 12.8%). In the Digoxin-Captopril Multicenter Study,¹⁶ digoxin, but not captopril, resulted in significant improvement in left ventricular ejection fraction; numerous other studies have shown improvement in left ventricular systolic function after digitalis administration.^{10,11,13,15,18} In contrast, there is some evidence to suggest intrinsic negative inotropism after acute administration of ACE inhibitors.¹⁹

Patients with CHF often show elevated levels of circulating catecholamines, which have been correlated with an adverse prognosis.²⁰ Gheorghade et al²¹ showed a decrease in circulating catecholamines after digitalis administration to patients with predominantly class III CHF; in this study, such a decrease was not observed after captopril administration. Similarly, Ribner et al¹² showed a decrease in both catecholamines and renin after digitalis administration to patients with CHF. Similar neurohumoral benefit has been observed after captopril administration as well.²²

Thus, available data does not show a clear advantage of vasodilator therapy over digitalis and diuretics in patients with predominately class II CHF.

Choice of vasodilator: When selecting a vasodilator regimen for patients with CHF, the decision is between an ACE inhibitor or a combination of isosorbide dinitrate and hydralazine. The combination of nitrates and hydralazine has several limitations, including a variable response rate of patients to the regimen,^{23,24} tolerance to long-acting nitrates,²⁵ a high incidence of adverse drug effects necessitating discontinuation of therapy^{6,24} and the need for multiple daily doses, which may interfere with patient compliance.²⁶ For these reasons, the optimal initial vasodilator for most patients with CHF is an ACE inhibitor; the preferred ACE inhibitor in this setting remains unknown.²⁷ The combination of isosorbide dinitrate and hydralazine should be reserved for patients who are not candidates for ACE inhibitors.

When initiating vasodilator therapy, certain caution must be exercised. We and others have showed that many patients fail to respond to vasodilator therapy;^{23,24,28} such nonresponsiveness is often associated with poor baseline hemodynamic variables, but generally cannot be noninvasively predicted. Vasodilator therapy may be associated with a significant incidence of adverse reactions, including occasional symptomatic hypotension and/or worsening of renal function.^{6,17,24,29} These and other considerations in vasodilator therapy are listed in Table III.

Asymptomatic left ventricular dysfunction: There is little available data on patients with truly asymptomatic chronic left ventricular dysfunction ("class I CHF"). Two recent studies have examined the use of captopril

for 1 year after acute myocardial infarction in patients with residual left ventricular dysfunction but no symptoms of CHF. Pfeffer et al³⁰ showed captopril to result in improved exercise capacity and hemodynamics in some patients at 1 year, but observed no improvement in left ventricular end-diastolic or end-systolic volumes as compared to placebo. Sharpe et al³¹ similarly observed no change in left ventricular end-diastolic volume after 1 year of captopril administration after acute myocardial infarction, but did show a small (7cc) decrease in end-systolic volume index, with a resultant increase in left ventricular ejection fraction. Digitalis has been shown to result in significant decreases in left ventricular end-diastolic pressure (19 to 10mm Hg) and increases in left ventricular stroke work (99 to 120 g-m) in convalescent patients after acute myocardial infarction.³² DeMots et al³³ showed that digitalis resulted in significant decreases in left ventricular end-diastolic and end-systolic volume index and an increase in left ventricular contractility in patients with severe coronary artery disease and no symptoms of CHF.

The clinical significance of these effects of ACE inhibitors and digitalis on left ventricular function in asymptomatic patients remain uncertain. Furthermore, results of the aforementioned studies may not be applicable to asymptomatic patients with left ventricular dysfunction not related to coronary artery disease. For these reasons, no specific recommendations for therapy can be made at this time for patients with asymptomatic left ventricular dysfunction; ongoing clinical trials may help to clarify these issues.

In conclusion, based on careful review of available data, our recommendations for the appropriate initial management of patients with chronic CHF are listed in Table IV.

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All Patients with Left Ventricular Systolic Dysfunction Should Be Treated with An Angiotensin-Converting Enzyme Inhibitor: A Protagonist's Viewpoint

Barry M. Massie, MD

In this report, I would like to support the proposition that most patients with significant left ventricular dysfunction, defined most easily as left ventricular dilatation with an ejection fraction <35 to 40%, should be treated with an angiotensin-converting enzyme (ACE) inhibitor; this includes patients exhibiting a wide spectrum of clinical symptomatology, ranging from the bedridden patient taking multiple medicines to patients who have never exhibited symptoms.

The goal of treatment varies with the clinical presentation. In refractory or severe congestive heart failure (CHF), a treatment can be considered effective if it is "palliative", as evidenced by a prolongation of survival and an improvement of quality of life (albeit of brief duration). In mild-to-moderate heart failure, an effective treatment should produce a more sustained decrease in symptoms, associated with an objective indicator of clinical benefit, such as enhanced exercise tolerance. If alternative effective therapies are available, an agent that improves prognosis is obviously preferable. In the asymptomatic patient, long-term treatment should prolong survival, delay the progression to symptomatic CHF or preserve left ventricular function. This report will present evidence that ACE inhibitors are beneficial in patients with each of these clinical presentations.

ACE inhibitors are part of the optimal management of severe and refractory congestive heart failure: As with all new therapies for CHF, the initial studies of ACE inhibitors examined the hemodynamic responses in patients with severe CHF despite optimal therapy with diuretics and digoxin. Consistent decreases in ventricular filling pressures and increases in cardiac output were documented¹; these decreases were associated with decreases in left ventricular size.² Unlike many agents, with ACE inhibitors, tolerance or loss of efficacy with time was rarely observed. Therefore, the decrease of hospitalizations and episodes of severe deterioration

during chronic treatment were not surprising (Figure 1).³

The most definitive study in this patient group is the Cooperative North Scandinavian Enalapril Survival Study.⁴ In this trial, 253 hospitalized patients who remained severely symptomatic despite therapy with diuretics, digoxin and, in many cases, vasodilators, were randomized to enalapril or placebo. The mortality rate in the patients treated with the ACE inhibitor was 40% lower at 6 months and 31% lower at 1 year (both $p < 0.002$). Of note, this beneficial effect was observed even in patients receiving other vasodilators (primarily nitrates). Furthermore, the ACE inhibitor group exhibited fewer symptoms and a significant decrease in heart size. Thus, the considerable experience with ACE inhibitors in severe CHF leaves no doubt that this group of patients should receive these agents.

Angiotensin-converting enzyme inhibitors are indicated in moderate congestive heart failure: In patients with less severe symptoms categorized as "moderate CHF," it is possible to examine objective endpoints such as exercise tolerance in addition to survival and symptoms. These patients have generally been studied by adding an ACE inhibitor while continuing treatment with diuretics and digoxin. Captopril was evaluated in a multicenter trial consisting of primarily New York Heart Association class III patients.⁵ During a 3-month period of randomized, double-blind treatment, the captopril group exhibited fewer withdrawals for worsening heart failure, greater improvement in symptoms and a decrease in New York Heart Association class compared to placebo. Exercise tolerance improved significantly with captopril, while remaining unchanged with placebo. Finally, in an "intent to treat" analysis, there were significantly fewer deaths in the captopril group (2 of 53 vs 11 of 52, $p < 0.01$), primarily as a result of a decrease in sudden deaths (1 vs 8).⁶ Treatment was well tolerated with few medication-related dropouts.

Other smaller controlled studies have confirmed these results with measurements of hemodynamics, exercise tolerance and clinical status using captopril and other ACE inhibitors.⁷⁻¹⁰ Therefore, there is little doubt that patients on diuretics and digoxin who remain symptomatic even with moderate exertion benefit from the addition of an ACE inhibitor.

Angiotensin-converting enzyme inhibitors are effective in mild congestive heart failure: Patients with mild CHF are, perhaps, the most difficult to classify

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and to study. However, this issue is addressed in a recently reported trial in which patients with predominantly class II CHF and relatively maintained exercise tolerance had captopril, digoxin or placebo added to their maintenance diuretic therapy.¹¹ Over a follow-up period of 6 months, exercise tolerance and clinical class both improved significantly with captopril compared to placebo. Most impressively, significantly fewer patients receiving captopril required increased diuretic dosages or hospitalizations and emergency room visits compared to the placebo group (Figure 2). These results indicate that maintaining patients with even mild CHF with diuretics alone is not optimal management for either minimizing symptoms or preventing subsequent deterioration.

This finding is further supported by a German study in which CHF patients with mild-to-moderate symptoms who were receiving diuretics and digoxin were randomized to captopril or placebo.¹² Again, progression to more severe heart failure was prevented by the ACE inhibitor.

Angiotensin-converting enzyme inhibitors appear beneficial in asymptomatic left ventricular dysfunction:

Before advocating treatment of asymptomatic individuals, one must have strong supporting data or at least a good rationale. Patients with dilated cardiomyopathy, characterized by a significantly decreased ejection fraction (<35%) and left ventricular dilatation have a relatively poor prognosis, even if they have few or no symptoms. This reflects the tendency of left ventricular enlargement and dysfunction to progress. Figure 3 schematically shows the natural history of dilated cardiomyopathy. Over time, patients tend to become increasingly symptomatic, although the rate of progression is unpredictable. Sudden death occurs throughout the course of the disease, but becomes more common as CHF becomes more severe.

The critical issue is the mechanism of progression. In some cases, the underlying disease (e.g., myocarditis or coronary disease) causes further damage. However, in other cases, a single or time-limited insult, such as myocardial infarction or myocarditis, leads to progressive

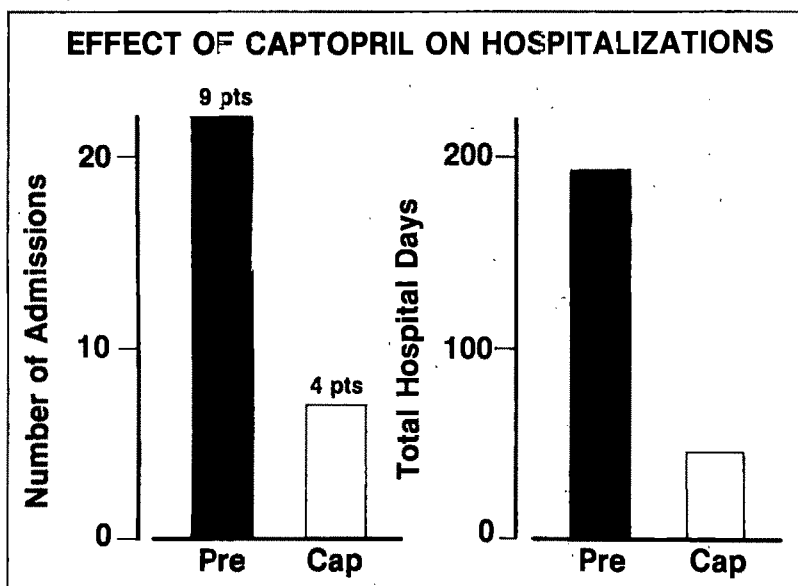


FIGURE 1. Decrease in hospitalizations and hospital days in group of 20 New York Heart Association class III and IV patients followed for a mean of 18 months on captopril (CAP) compared to an identical period before (Pre) angiotensin-converting enzyme inhibitor therapy. Nine patients were hospitalized a total of 22 times for 195 days before Cap; taking Cap, only 4 patients were hospitalized 7 times for a total of 38 days. Modified with permission from *Am J Cardiol* 1984;53:1316-1320.

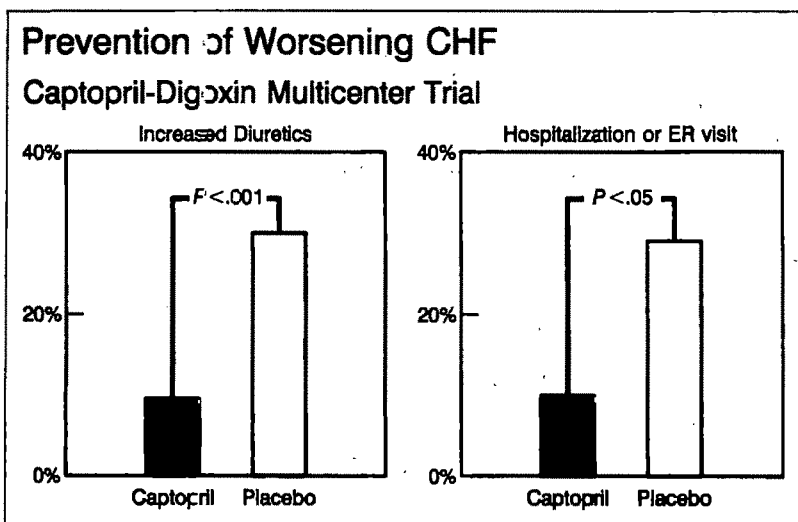


FIGURE 2. Lower incidence of requiring increases in diuretic dosages and decreased number of hospitalizations and emergency room (ER) visits for heart failure in a group of mild-to-moderate heart failure patients treated with captopril compared to a similar group managed on diuretics alone. CHF = congestive heart failure. Modified with permission from *JAMA* 1988;259:539-544.

dysfunction. There are a number of possible explanations for this process. Left ventricular remodeling after the initial injury may distort myocardial geometry so that systolic function is impaired. Elevated wall stress may lead to further dilatation and rapid progression. Initially, compensatory myocyte hypertrophy may itself lead to energetic failure.¹³ Neurohormonal activation may lead to excessive myocardial stimulation or other deleterious consequences.¹⁴ Finally, circumstantial evidence suggests that even in primary cardiomyopathy, imbalances between myocardial oxygen supply and demand may lead to subendocardial ischemia and necrosis.¹⁵ Unloading the left ventricle and decreasing its volume overload may protect it from further damage. Because of the potentially negative impact of excessive neurohormonal activity, an agent that interdicts these effects may be optimal.

This rationale is given some credence by studies examining the effect of ACE inhibition on the progressive left ventricular dilatation and dysfunction that follow large myocardial infarctions, which may represent a

paradigm for other forms of heart failure. Two studies have randomized such patients to an ACE inhibitor or placebo (and in 1 study, furosemide). In one, the captopril group exhibited a decrease in left ventricular size and an increase in ejection fraction compared to groups treated with either placebo or furosemide.¹⁶ In the second study, left ventricular function and size remained stable with captopril but deteriorated with placebo, again suggesting a protective effect of ACE inhibitors.¹⁷ If the previously postulated mechanisms for CHF progression are operative, it is reasonable to speculate that ACE inhibitors may have a preventive role in asymptomatic or mildly symptomatic dilated cardiomyopathy. Of course, further evidence is much needed and is being collected.

Asymptomatic patients fall into 2 subgroups—those receiving treatment for previously symptomatic CHF and those who have never had symptoms. I suspect many of the former are limited in more strenuous activities and that they are likely to exhibit a more fluctuating and progressive picture. Use of ACE inhibitors in

FIGURE 3. Natural history of congestive heart failure (CHF). Although rate varies, most patients exhibit progressive symptoms and left ventricular dysfunction. Sudden death may occur at any stage, but becomes more frequent in advanced CHF. Mechanisms of progression are unclear and probably highly variable. In part, CHF progresses as a result of ongoing damage and ischemia. Markedly elevated wall stress that characterizes dilated cardiomyopathy may further impair cardiac performance. Neurohormonal activation may play a role in both disease progression and sudden death.

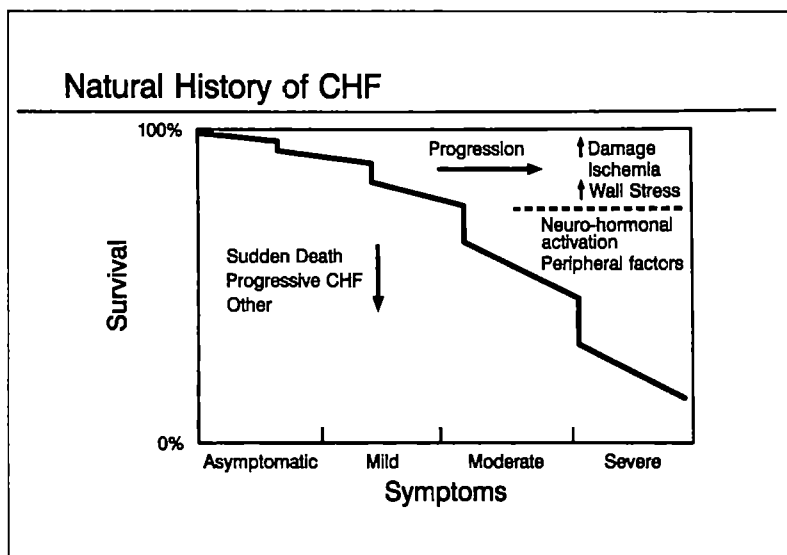
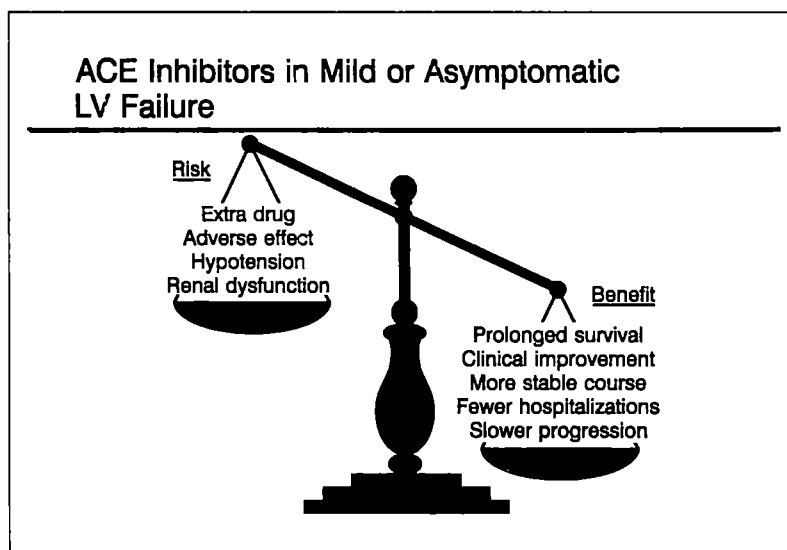


FIGURE 4. In determining whether to initiate angiotensin-converting enzyme (ACE) inhibitors, an individualized assessment of potential benefits and risks must be made. Benefit is clear in symptomatic patients and potentially important in those without symptoms. Risks of ACE inhibitors are minimal. Hence, these considerations indicate that most patients with congestive heart failure should receive an ACE inhibitor. LV = left ventricular.



this group is warranted on the basis of the positive data in mild CHF, assuring that left ventricular function remains abnormal. While the rationale for starting ACE inhibitors in totally asymptomatic individuals makes good sense, this approach is, at the present time, investigational. Nonetheless, just as we revascularize some patients with critical coronary lesions who are not symptom-limited, I would advocate using ACE inhibitors in asymptomatic patients with more severe left ventricular dysfunction and dilatation, who, after all, have mortality rates comparable to asymptomatic left main coronary disease.

Angiotensin-converting enzyme inhibitors are beneficial in congestive heart failure by a number of mechanisms: This point is of considerable importance. If one accepts a narrow view that the only action of ACE inhibitors is to prevent the conversion of circulating angiotensin I to angiotensin II, with resulting vasodilation and decreased aldosterone secretion, it is difficult to justify the use of ACE inhibitors in mild-to-moderate CHF, where plasma-renin activity is often normal. Yet, they clearly work in these patients and their hemodynamic and clinical effects are often dissociated from measurements of plasma-renin activity. Certainly, this discrepancy may reflect intermittent activation of neurohormonal systems during periods of hemodynamic or other stress. However, it has also become apparent that these agents have multifaceted beneficial effects, including those listed in Table I.

The ubiquity of tissue renin-angiotensin systems is now well accepted,⁸ although their clinical importance remains to be elucidated. It is certainly possible that inhibition of intrarenal or myocardial angiotensin production may be beneficial in some patients with CHF. We now appreciate the ability of ACE inhibitors to inhibit tissue-kinin metabolism, which in turn stimulates prostaglandin production. Prostaglandins play a significant role in ACE inhibitor-induced vasodilation.¹⁹ Particularly intriguing are the interactions between the renin-angiotensin system and the sympathetic nervous system.²⁰ In addition to the role of the latter in producing undesirable vasoconstriction, the sympathetic nervous system may play a role in arrhythmogenesis and even cause myocardial damage; ACE inhibitors may "down-regulate" the sympathetic nervous system in CHF, thus accomplishing what has been attempted investigational with β blockers. ACE inhibitors also improve coronary hemodynamics and myocardial metabolism,²¹ although whether this is due to coronary vasodilation or decreased myocardial oxygen requirements is not known.

The beneficial effects of ACE inhibitors on central hemodynamic measurements have been well characterized.^{1,2} The combined decrease of left ventricular preload and afterload is necessary to optimize cardiac performance in most patients with CHF and produces the greatest decrease in wall stress, an action that may delay the progression of CHF. We now recognize that peripheral effects may be crucial as changes in central hemodynamics in ameliorating the syndrome of CHF. Changes in peripheral blood flow and skeletal muscle

TABLE I Potentially Beneficial Actions of the Renin-Angiotensin System in Congestive Heart Failure

Neurohormonal
Inhibition of circulating RAS
Decreased aldosterone secretion
Inhibition of tissue RAS
Stimulation of prostaglandin production
Decreased sympathetic nervous system activity
Central hemodynamic
Decreased systemic resistance (afterload)
Decreased ventricular filling pressures (preload)
Peripheral effects
Increased peripheral blood flow
Improved muscle metabolism
Increased renal blood flow
Improved myocardial metabolism
Decreased arrhythmias

RAS = renin-angiotensin system.

metabolism and function are important determinants of exercise intolerance in CHF.²² These can be reversed by ACE inhibitors and these effects may be in part responsible for improved exercise capacity.

Finally, several studies have indicated that ACE inhibitors may decrease ventricular ectopy in CHF.^{8,10,11} The previous discussion suggests several potential mechanisms for such an effect, including increases in serum and total body potassium, decreased adrenergic stimulation, decreased heart size, prevention of myocardial ischemia or prevention of progressive myocardial damage. This "antiarrhythmic" effect may play a role in the improved survival observed with ACE inhibitors.

Angiotensin-converting enzyme inhibitors are more effective than direct vasodilators: The ACE inhibitors are often classed together with other agents that produce vasodilation, such as the nitrates, hydralazine, alpha-adrenergic blockers and calcium antagonists. From the previous discussion, it can be seen that this is inappropriate. Indeed, vasodilators often activate the renin-angiotensin system and sympathetic nervous system, which may explain some of the tolerance that develops to their effect. As opposed to the data with ACE inhibitors, evidence that these vasodilators improve symptoms in CHF patients is very limited and, at best, inconclusive. Even the Veterans Administration Heart Failure Trial study, which showed improvement in survival with the combination of hydralazine and isosorbide dinitrate,²³ failed to show a substantial improvement in exercise tolerance.²⁴ Thus, ACE inhibitors should be differentiated from other vasodilators and are clearly the agents of choice for improving cardiac performance by altering left ventricular loading conditions.

Angiotensin-converting enzyme inhibitors versus digoxin—a nonissue: The relative efficacy of ACE inhibitors and digoxin is often debated,^{25,26} but, in my opinion, is not relevant to this report. I have presented data showing that ACE inhibitors are beneficial in all classes of symptomatic CHF patients. Studies have been conducted with and without a background of digoxin therapy with equally positive results.

I also believe digoxin is an effective agent in the treatment of CHF, although this point remains contro-

versial in patients in sinus rhythm. One of the reasons for the continuing debate is that digoxin is most effective in patients with advanced CHF, marked left ventricular enlargement and severe left ventricular dysfunction.^{27,28} In milder CHF, it has been difficult to show a beneficial response.²⁶ The effect of digoxin on survival in CHF has not been studied. Post hoc analyses have raised a question about increased mortality rates in patients with ischemic heart disease, but these have not been substantiated in other studies. However, other positive inotropic agents, such as the phosphodiesterase inhibitors and adrenergic stimulants, have been associated with trends toward an increased mortality rate.²⁹

For this report, it is sufficient to state that there is no evidence to indicate that digoxin improves survival in symptomatic patients or prevents the progression of left ventricular dysfunction in asymptomatic patients. Therefore, one can readily argue that these patients should all receive an ACE inhibitor, whether or not they are being treated with digoxin.

Angiotensin-converting enzyme inhibitors have a favorable benefit to risk ratio: In the final analysis, physicians must determine whether to prescribe a medicine based upon their assessment of the benefit to risk ratio in each patient and whether or not the agent is specifically approved for this indication. The ACE inhibitors are remarkably well tolerated, even in fragile CHF patients. The major risks are excessive hypotension and functional renal insufficiency. These occur most commonly in patients with preexisting renal dysfunction and hypotension and can usually be avoided by careful monitoring and adjustment of ACE inhibitor dosages and accompanying medications. The benefits, both proven in symptomatic patients and potential in asymptomatic individuals, are great. I think the balance of benefits and risks clearly supports the use of ACE inhibitors in most of these patients (Figure 4).

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Nitrates Are Effective in the Treatment of Chronic Congestive Heart Failure: The Protagonist's View

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Nitrates have gained wide acceptance as adjunctive therapy in the management of congestive heart failure (CHF) since early studies showed that these agents, whether administered intravenously, sublingually, orally or transcutaneously, produced a striking decrease in ventricular filling pressure and a modest increase in cardiac output.¹⁻³ The favorable hemodynamic effects have been attributed to an increase in venous capacitance induced by venodilation combined with a decrease in vascular resistance induced by arteriolar dilation. An effect to increase large artery compliance probably plays an important role in decreasing impedance to left ventricular emptying.⁴

Proof of clinical efficacy on the signs and symptoms of CHF has been more difficult to achieve. We observed in 1974⁵ that chronic isosorbide dinitrate therapy could maintain cardiovascular stability long-term in a patient with severe left ventricular failure who had become dependent on intravenous nitroprusside and who deteriorated when placebo was substituted for isosorbide dinitrate. This experience convinced us that oral nitrates could be effective therapy in at least some patients with CHF, but this "N of 1" experiment⁶ was hardly adequate to convince scientists committed to large sample sizes and statistical validation. Indeed, even if this "experiment" had been more critically designed to include several active and placebo treatment periods, it would not have addressed the issue of the frequency of a favorable effect, the proper dosing of the drug or its tolerability. Furthermore, the possibility that the placebo-associated deterioration represented a rebound effect from nitrate withdrawal rather than simply the removal of an effective agent could not be excluded.

Only a few studies of modest sample size have been carried out to evaluate the effect of oral nitrates on signs and symptoms in patients with CHF.⁷⁻¹⁰ In each of these well controlled, double-blind studies, the trend in exercise tolerance, perceived symptoms and morbid events has favored isosorbide dinitrate over placebo. However, because of the small size of each of these studies (a total of 47 patients treated with the nitrate), the beneficial effect on exercise tolerance barely achieved the 95% confidence limits traditionally re-

quired to make results acceptable to the medical community.

At least the following 2 factors must be considered in assessing the published studies on clinical efficacy of oral nitrates for CHF: use of peak exercise tolerance as a therapeutic endpoint; economic factors limiting studies of efficacy.

Peak exercise tolerance: Because impaired left ventricular functional response to exercise and decreased exercise capacity are hallmarks of the syndrome, it is appropriate that exercise tolerance be used as a guide to therapeutic efficacy in CHF. The problem with exercise testing, however, is that the only objective endpoint has been peak capacity during a test of progressively increasing loads. The subjective endpoint of fatigue and dyspnea now can be satisfactorily replaced by on-line measurement of oxygen consumption and carbon dioxide production. These measurements provide objective evidence that the anaerobic threshold has been surpassed and they also provide a quantitation of work done by the peak oxygen consumption achieved.¹¹ However, peak exercise capacity may not be the appropriate endpoint for therapeutic efficacy in CHF. For example, this measurement does not quantitate the comfort with which a patient can carry on submaximal work, a possibly more appropriate guide to clinical symptomology in CHF. Even drugs assumed to be effective in heart failure do not always significantly improve peak exercise capacity. Increases have been shown in some controlled trials using converting-enzyme inhibitors,^{12,13} but in other studies, some of them including large numbers of patients, the ACE inhibitors have not produced a statistically significant increase in maximum exercise.¹⁴ Other vasodilator interventions have also failed to exhibit an increase in exercise capacity in controlled trials.^{15,16}

A possible dissociation between changes in maximal and submaximal exercise capacity may be particularly pertinent with the nitrates. The first dose of isosorbide dinitrate produces a favorable hemodynamic effect at rest and during submaximal exercise, but the beneficial hemodynamic effect appears to disappear at matched peak workloads.¹⁷ The lower pulmonary capillary pressure and higher cardiac output at submaximal workloads might therefore allow modest work to be done longer or with less dyspnea and fatigue without an improvement in peak capacity to deliver oxygen to working skeletal muscle.¹⁸ Unfortunately, however, studies using quantitative submaximal tests capable of detecting an improvement in exercise function in response to nitrates or any therapy have not been designed and validated.

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It thus seems imprudent to base efficacy of a therapy for CHF solely on the basis of its effect on peak exercise capacity. Nonetheless, however, given the small number of patients studied, the nitrates appear to have exerted remarkably favorable effects on this endpoint when compared to the responses to other drugs.

Economic factors: Study of drug therapy for CHF is fueled by the pharmaceutical industry whose market share and profits will be augmented by regulatory body approval of a new drug. Drugs with a long patent life and consequent high price tag are the agents in which the high cost of drug development and approval can be justified. Unfortunately, the Food and Drug Administration has no mechanism by which they can help decrease the cost of developing a new use for a generic drug whose sales may not be perceived by a drug company as likely to match the costly development.

Such is the dilemma of the nitrates for heart failure. So many nitrate preparations in so many forms manufactured by so many pharmaceutical companies are available that no single company has felt it prudent to undertake the large clinical trials necessary to satisfy the usual standards of proof that long-term nitrate therapy when added to digitalis and diuretics can improve signs, symptoms and quality of life in patients with heart failure.

Hydralazine-isosorbide dinitrate combination: Our early trials with oral vasodilator regimens were aimed at developing a long-term therapy that could replicate the hemodynamic effects of infusion of sodium nitroprusside.¹⁹ Because nitrates appeared to mimic the venous capacitance effects of nitroprusside but not the arterial dilating effect, we used a known arterial dilator, hydralazine, in combination with isosorbide dinitrate to produce the desired hemodynamic response.²⁰ This combination was quite well tolerated and therefore allowed the design of a definitive long-term multi-center trial to test the potential benefits of such an apparently ideal vasodilator regimen on the course of CHF. An alternative vasodilator regimen, prazosin, was included in the trial because early studies had shown this drug also produced a balanced dilator effect on both the venous and arterial vasculature.²¹

As has previously been reported,²² the hydralazine-isosorbide dinitrate regimen had a favorable effect on survival and also produced an increase in left ventricular ejection fraction²² and an improvement in exercise tolerance²³ when compared to the placebo therapy. Prazosin did not exert any demonstrable beneficial effects. Because the effective Veterans Administration Heart Failure Trial therapy included 2 vasodilator drugs, it is not possible to prove that both agents are necessary for the beneficial effect. Until similar studies are undertaken with each agent alone (an unlikely event) the prudent approach is to assume that the favorable hemodynamic effects of the combination are translated into long-term benefits. Use of the 2 drugs together is made more acceptable by the long history of safety of these 2 generic drugs and by their low cost. It is our position that nitrates may be effective on some of the signs and symptoms of heart failure when added alone to digitalis and

diuretics, but the definitive trial showed efficacy when nitrates are used in combination with hydralazine. Therefore, the recommended vasodilator regimen for heart failure should ideally include both drugs.

Nitrate tolerance: Nitrate skeptics have raised concern that chronic therapy may result in attenuation of the vascular actions of the nitrate and loss of clinical effectiveness. It is certainly well recognized clinically that the vasodilator headache induced by nitrates wanes with continued administration of the drug. It has also been amply shown in several studies that in some patients, the hemodynamic effects of intravenous, transdermal, sublingual and orally administered nitrates may become attenuated during continuous or repeated dosing.^{24,25} These studies have clearly shown the potential for tolerance to some of the circulatory effects of nitrates, but they cannot exclude a continued response in some patient populations with some dosing regimens and furthermore, these hemodynamic studies cannot exclude a favorable clinical response even in the absence of a measurable effect on the parameters studied. Further exploration of the optimum dosing regimen for chronic nitrate therapy is clearly needed, but the ultimate proof for efficacy must reside in clinically measurable endpoints not on hemodynamic indexes that are well recognized to bear a poor relation to symptoms and life expectancy in heart failure.²⁶

Optimal dosing of nitrates: The ideal regimen for chronic nitrate therapy is still not established. The traditional principle has been to use the highest tolerated dose to achieve maximal benefits and to choose a regimen that comes as close as possible to maintaining a vascular effect throughout the 24-hour day. This principle may now be questioned for at least the following 2 reasons: the dose-response for different vascular effects may be dissimilar, so that the highest tolerated dose may not be the optimal dose for all clinical indications; and the problem of tolerance may be mitigated by providing a drug-free interval during the day so that nitrate efficacy can be restored.

Transdermally administered nitroglycerin appeared initially to be an ideal means of therapy because constant blood levels could be achieved over long periods of time. More recent experience suggests that constant blood levels may encourage early development of tolerance. Indeed, in patients with heart failure, the hemodynamic effect of transdermal nitroglycerin appears to wane after about 6 hours.²⁷ Nonetheless, rebound vasoconstriction after withdrawal of the nitroglycerin patch indicates that some physiologic effect of the nitrate was persisting despite the apparent attenuation of the measured vascular actions. A recent Food and Drug Administration-sponsored study of transdermal nitroglycerin in patients with angina showed loss of clinical efficacy even to high transdermal doses (personal communication).

Oral therapy yielding fluctuating blood levels appears to be a more attractive regimen. In Veterans Administration Heart Failure Trial, the dose of isosorbide dinitrate was 40 mg 4 times daily, a dose chosen because of the hemodynamic response and duration of ef-

fect after single doses of the drug. In this trial, the average interval between the nighttime and morning doses was 8 to 10 hours. A longer dosing interval has been suggested by others,²⁸ but the long-term beneficial effect in the Veterans Administration Heart Failure Trial of this therapeutic regimen has encouraged us to continue to use it clinically.

Future of nitrate therapy for heart failure: One of the most exciting developments in the nitrate field has been the recent evidence that nitric oxide, the active product of nitrodilator drugs, is also the active substance released from endothelium in response to a variety of physiologic and pharmacologic stimuli.²⁹ Furthermore, evidence has accumulated that this endothelial-derived relaxing factor is deficient in atherosclerotic coronary arteries and in the peripheral vasculature in other disease states.³⁰ Nitrates may therefore now be viewed as endogenous vasodilators and their administration may actually be restoring deficient endogenous nitric oxide.

Worldwide use of nitrates as part of a primary vasodilator regimen for CHF may be waning because of the growing use of angiotensin-converting enzyme inhibitors. The efficacy of angiotensin-converting enzyme inhibitors in CHF has been shown in several well-controlled trials and their use has been widely stimulated by aggressive marketing efforts supported by the manufacturers of these agents. Nitrates have not been the beneficiaries of the multiple studies or the effective marketing effort.

It may be appropriate now to reexamine the issue of nitrates (or preferably nitrates plus hydralazine) versus angiotensin-converting enzyme inhibitors in the treatment of CHF. The angiotensin-converting enzyme inhibitors are unique agents whose favorable effects may be heavily dependent on actions other than vasodilation. They have clear-cut metabolic effects to retain potassium and magnesium and the suppression of angiotensin II may inhibit vascular and myocardial hypertrophy. Their vasodilator effect in terms of acute hemodynamic response appears to be less potent than that of hydralazine and isosorbide dinitrate. The future use of nitrates, therefore, may be as part of a vasodilator regimen to supplement the beneficial effects of angiotensin-converting enzyme inhibitors in the treatment of CHF.

For patients with CHF to have the benefit of nitrate therapy, approval of this form of therapy by the Food and Drug Administration is necessary. The Veterans Administration Heart Failure Trial study has provided adequate evidence for efficacy of the nitrate-hydralazine regimen. The agency may need to modify their usual standards for approval of drug combinations to allow this study to impact upon life expectancy of the millions of Americans who have this syndrome.

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Should Complex Ventricular Arrhythmias in Patients with Congestive Heart Failure Be Treated? A Protagonist's Viewpoint

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The prognosis in congestive heart failure (CHF) is poor. About 50% of patients die within 5 years and almost one-half of these deaths are sudden.^{1,2} Thus, prophylactic management strategies are needed.

Importance of complex ventricular arrhythmias in congestive heart failure: High-grade, complex ventricular arrhythmias occur in most patients with a history of CHF and are associated with an increased risk of mortality, particularly sudden death. In 1 review,¹ couplets and/or multiformed complexes occurred in 87% of patients and runs of ventricular tachycardia occurred in 54% of CHF patients. In another review, unsustained ventricular tachycardia increased the risk of mortality by a factor of 2.8 (range, 1.3 to 5.4).² The risk of arrhythmias on mortality is also independent of ejection fraction.³⁻⁵ Besides ambient arrhythmias,^{3,4} arrhythmia inducibility at electrophysiologic study is a strong risk marker for mortality⁵ and may be a better guide to therapy than ambulatory monitoring.⁶ The presence of a late potential on signal-averaged electrocardiography also causes an increased risk of ventricular tachyarrhythmias and sudden death and this risk is greater than and independent of the presence of spontaneous arrhythmia.⁷

Therapy other than traditional antiarrhythmic drugs: **MULTIPLE RISK FACTORS:** If complex ventricular arrhythmias in patients with ventricular dysfunction represent a risk factor for mortality, can treatment of arrhythmias decrease the risk of sudden death? Vulnerability is undoubtedly influenced by multiple factors. In addition to arrhythmia, ventricular dysfunction, myocardial ischemia, neurogenic and endocrine factors, metabolic and blood gas imbalance and drugs, including antiarrhythmic drugs, may be risk factors. These multiple risk factors suggest a multipronged approach.

GENERAL TREATMENT APPROACH: First, the cause and extent of underlying heart disease should be determined and reversible factors (e.g., ischemia, myocarditis, toxins) corrected. Uncompensated CHF should be treated. Diuretic dosage should be carefully titrated and adequate electrolyte replacement given. Vasodilator therapy, often preferably a converting-enzyme inhibitor, should be considered. An oral or cutaneous nitrate preparation should also be considered, especially when angina

or dyspnea is present. Digitalis is reserved for atrial fibrillation or a low-output syndrome with a dilated heart and a ventricular gallop.

ARRHYTHMOGENIC EFFECTS OF CONGESTIVE HEART FAILURE THERAPY: The treatment of CHF may itself be arrhythmogenic. Diuretics frequently cause electrolyte imbalance. Digitalis may cause toxic arrhythmias. Other inotropes, including the new vasodilator-inotropes, have proarrhythmic risk and may worsen long-term prognosis.⁸ Direct-acting vasodilators cause reflex increases in sympathetic tone and renin release, predisposing to ventricular arrhythmias. An important goal is to prevent, minimize or reverse these arrhythmogenic effects.

CONVERTING-ENZYME INHIBITION AND ARRHYTHMIAS: Arrhythmia decrease is among the effects of converting-enzyme therapy. Captopril has been shown to decrease ventricular ectopic frequency by one-third and to suppress runs by two-thirds.⁹ These effects were associated with decreases in plasma norepinephrine and increases in potassium levels to well within the therapeutic range. A beneficial effect of converting-enzyme inhibition on mortality has also recently been shown. In the Cooperative North Scandinavian Enalapril Survival Study of enalapril versus placebo in 253 patients with class IV CHF, treatment decreased mortality by 41% at 6 months ($p < 0.005$) and by 31% at 12 months ($p = 0.01$).¹⁰ A favorable but nonsignificant trend for sudden death was noted. In a multicenter captopril study,¹¹ total mortality was decreased from 11 to 2 and sudden death mortality decreased from 8 of 52 to 1 of 53 ($p < 0.05$).¹¹

A ROLE FOR BETA BLOCKADE IN SELECTED PATIENTS?: It is well known that β blockade may exacerbate CHF by decreasing contractility, increasing ventricular volumes and suppressing compensatory sympathetic activity. On the other hand, β blockade may also improve cardiac dysfunction by balancing oxygen demand and supply, providing antiarrhythmic activity and decreasing the cardiotoxicity of chronic catecholamine stimulation.

In postinfarction patients, β blocker therapy decreases mortality not only in those with preserved ventricular function but also in those with the most severe left ventricular dysfunction allowed study entry (Table I). In the β blocker Heart Attack Trial, the relative decrease by propranolol in cardiovascular death from all causes was 32% in those with a history of CHF, compared with 21% in those without.¹² Of particular note, sudden death was decreased 47% in CHF patients, compared with only 13% in others. The risk of CHF caused

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TABLE I Decrease in Mortality of Beta Blockade in Patients with Congestive Heart Failure in B-HAT Study

Event	Relative Decrease by Propranolol	
	CHF (%)	No CHF (%)
Cardiovascular death (any)	32	21
Sudden death	47	13
Nonfatal MI	42	6

B-HAT = β -Blocker Heart Attack Trial; MI = myocardial infarction.
Data adapted from Chadda et al.¹² with permission of the publisher.

by therapy was surprisingly modest. The impressive effect on sudden death suggests an antifibrillatory action. Beta-blocker therapy should be considered in patients with ischemic heart disease and compensated ventricular dysfunction. Low-dose initiation and gradual up-titration may improve tolerance and decrease adverse effects.

Beta-blocker therapy was also suggested for dilated cardiomyopathy by the Göteborg Swedish Group 15 years ago, based on observational studies.¹³ Given in small, gradually increasing doses, metoprolol was generally well tolerated and improved functional status over a period of weeks to months. Discontinuation was often accompanied by deterioration, with restoration of stability after resumption of therapy. Subsequent randomized studies in compensated class II/III patients have confirmed the potential for functional benefit.^{14, 5} Additional studies, many underway or being planned, will further assess the role of β blockade in compensated CHF.

Treating congestive heart failure patients with antiarrhythmic drugs: ANTIARRHYTHMIC DRUG CLASSES: Four general antiarrhythmic drug actions, which define separate classes, result from differing membrane blocking actions, that is, on sodium channels (class I), β -adrenergic receptors (class II), potassium channels (class III), or calcium-entry channels (class IV).

COMPARATIVE ANTIARRHYTHMIC EFFICACY: Using a definition of $\geq 75\%$ decrease in ventricular premature complexes on ambulatory recording, efficacy has been shown for available class IA agents (quinidine family) in approximately two-thirds of patients, for class IB agents (lidocaine family) in about half and for class IC agents (flecainide, encainide) in about 80%. About half respond to propranolol, up to two-thirds respond to the class II/III agent sotalol and over three-fourths respond to amiodarone. Using an electrophysiologic end point (arrhythmia inducibility) for patients with sustained ventricular tachyarrhythmia leads to lower rates of efficacy (20 to 30%). A new agent, sotalol, promises to be somewhat more effective (30 to 40%).

NONCARDIAC ADVERSE EFFECTS: Noncardiac intolerance rates are drug-specific. Agents currently in class IA have moderately high intolerance rates (about 25 to 30%), for varying reasons. Class IB drugs are poorly tolerated (30 to 40% dropout rate), primarily because of reversible neurologic or gastrointestinal toxicity. Class IC agents have the lowest rates (only 5 to 15% require discontinuation). Beta blockers are free of organ toxic-

TABLE II Outcome of Treatment in Patients with Malignant Ventricular Arrhythmias

Evaluation Method	Responders		Nonresponders	
	n	3-Year Mortality	n	3-Year Mortality
Holter/ETT ¹⁸	98	14%	25	85%
EPS ¹⁹	103	20%	102	68%

ETT = exercise treadmill testing; EPS = electrophysiologic study.

ty, but excessive bradycardia, fatigue, dyspnea and CHF may limit their use. The side effects of amiodarone are dose- and time-dependent. Even with lower dose therapy, side effects may appear after long-term use. The risk of potentially serious pulmonary toxicity is approximately 2 to 3% per year or 10 to 15% by 3 to 5 years.

NEGATIVE INOTROPIC EFFECTS: The degree of negative inotropy, of particular importance in patients with CHF, varies by agent. Disopyramide has the greatest negative inotropic potential, followed by flecainide and the β blockers. Encainide may also show important effects in CHF.¹⁶ Quinidine and mexiletine have modest or negligible effects in most settings. Because CHF patients are frequently only marginally compensated, the addition of a drug with significant negative inotropic potential may lead to important decompensation in mechanical and electrical function.

PROARRHYTHMIC POTENTIAL: All antiarrhythmic drugs may exacerbate arrhythmias in some patients (2 to 15%). Patients with CHF not only show the highest risk of mortality but are also at greatest risk for proarrhythmia, especially when left ventricular dysfunction is combined with a history of sustained ventricular tachycardia or ventricular fibrillation.¹⁷ For class I agents, the risk is approximately proportional to antiectopic potency; mexiletine and tocainide have mild to moderate potential, quinidine and other class IA agents have moderate potential and class IC agents (encainide, flecainide) have relatively high potential. Amiodarone and the β blockers have the lowest potential for arrhythmia exacerbation. In CHF patients, a significant proarrhythmic risk could overwhelm any beneficial potential of treatment.

ANTIARRHYTHMIC THERAPY FOR PATIENTS WITH MALIGNANT VENTRICULAR ARRHYTHMIAS: Patients who have experienced a life-threatening ventricular tachyarrhythmia are known to be at high-risk for recurrence, unless the event was precipitated by a transient, nonrecurring stimulus (such as acute myocardial infarction). Observational studies using both noninvasive and invasive methods suggest that patients responding to an antiarrhythmic regimen have a better prognosis than those not responding^{18, 19} (Table II). Among 123 patients with malignant ventricular arrhythmias (most also had ventricular dysfunction), 3-year mortality was substantially lower (14%) if the antiarrhythmic drug regimen suppressed arrhythmias by Holter monitoring and exercise testing than if it did not (85% mortality).¹⁸ Combination therapy with a β blocker was emphasized.

Several studies that have used the electrophysiologic end point have also shown a better prognosis for drug regimens associated with a successful response. In 1 study, a 20% 3-year mortality was observed among drug responders ($n = 103$), compared with a 68% 3-year mortality among nonresponders ($n = 102$).¹⁹ Therapy in these patients actually appears to prevent arrhythmias, rather than only mark "good risk" patients, because a high arrhythmia recurrence rate has been observed if drugs are discontinued. These data argue persuasively for therapy in this patient group, using a carefully monitored approach.

TREATMENT OF ASYMPTOMATIC ARRHYTHMIAS: Whether therapy should be given for asymptomatic ventricular arrhythmias, and, if so, in what form, is an important issue. Prior antiarrhythmic drug mortality studies do not provide a firm basis for prophylactic usage of antiarrhythmic drug regimens.²⁰ These trials are limited in size and design and have shown unfavorable²⁰ and favorable trends.²¹ They have included patients both with and without a CHF history.

However, specific support for antiarrhythmic therapy in CHF patients being treated with vasodilator-inotropic agents is provided by observations from the University of California, San Francisco.²² Sudden death rates were lower in treated patients (most commonly, amiodarone was used), although total mortality rates were similar.

Further support for the use of amiodarone is provided by Cleland and Dargie,²³ who evaluated variables predictive of mortality in 132 CHF patients followed prospectively for a mean of 21 months. Frequent premature ventricular complexes, nontreatment with amiodarone, low mean arterial pressure and a diagnosis of coronary artery disease were associated with a poor prognosis. Amiodarone treatment significantly improved prognosis ($p < 0.01$), decreasing sudden death from 45 to 15% (Figure 1). The study was not randomized, but this promising result deserves further evaluation.

CARDIAC ARRHYTHMIA PILOT AND SUPPRESSION TRIALS: The Cardiac Arrhythmia Pilot Study²⁴ showed that postinfarction arrhythmias could be effectively suppressed; the response rate in patients with low ejection fractions, although not optimal, was reasonably well maintained. Adverse events (such as unsustained tachyarrhythmia and CHF) were increased in those with low ejection fraction, but were observed with equal frequency in the placebo and active treatment groups.²⁴ The Cardiac Arrhythmia Suppression Trial was subsequently begun to test the hypothesis that arrhythmia mortality/cardiac arrest rates might be favorably affected by suppression of prognostically important ventricular arrhythmias in postinfarction patients with left ventricular dysfunction. The 3 drugs effectively suppressing ventricular ectopy in the pilot study (encainide, flecainide and moricizine) were selected for evaluation.

IMPLICATIONS OF THE CARDIAC ARRHYTHMIA SUPPRESSION TRIAL: On April 17, 1989, the encainide and flecainide treatment limbs were terminated because of an adverse effect on total and sudden death mortality.²⁵ Total event rates were 56 and 22, and sudden death and car-

diac arrest event rates, 33 and 9, respectively, in the active ($n = 730$) and placebo ($n = 725$) groups (risk ratios 3.6, 2.5). An adverse outcome was consistently observed in various subgroups, including depressed ejection fraction ($<30\%$). Presumably, these 2 drugs decreased the threshold for ventricular fibrillation, although they also suppressed spontaneous ventricular ectopy to a high degree ($\geq 80\%$). The study was continued for the moricizine limb, which did not show an adverse effect. This result for the moricizine limb leaves open a strong possibility that a beneficial effect for specific antiarrhythmic therapies (other than class IC) may still be observed.

On the basis of these early results, it appears that suppression of ventricular premature complexes is not sufficient as a predictor of sudden death decrease. However, suppression may still be necessary for optimal prevention. The Cardiac Arrhythmia Suppression Trial does stress the need to evaluate each drug and drug class separately for mortality effects, however.

ANTIFIBRILLATORY VERSUS ANTIECTOPIC EFFECTS: The Cardiac Arrhythmia Suppression Trial results indicate the complexity of the problem of preventing arrhythmic death.²⁵ In order to be effective, therapy may need to have a beneficial effect on the arrhythmia substrate as well as on spontaneous ectopy. It is still possible, if not likely, that prognostically important arrhythmias are "triggering events" for more malignant tachyarrhythmias, rather than just extraneous risk markers. These triggering beats may act on a myocardial substrate that shows varying degrees of vulnerability for a sustained arrhythmic event. The effects of therapy on substrate

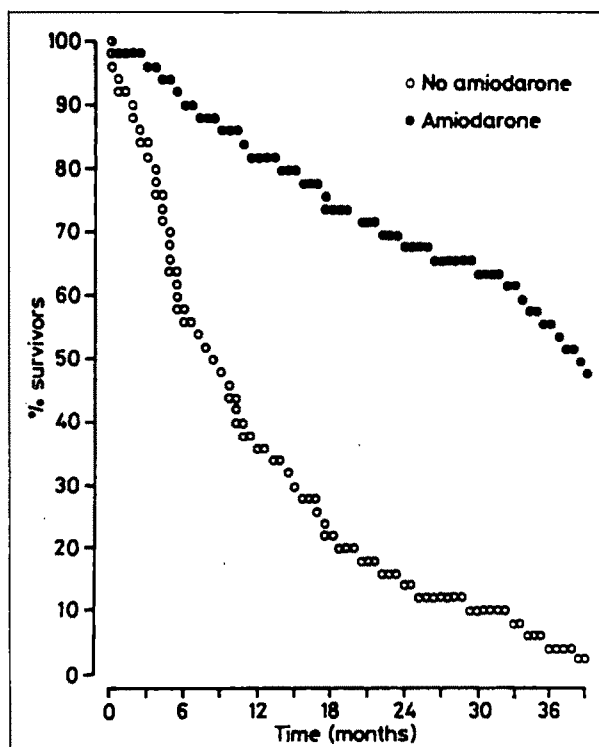


FIGURE 1. Estimated survival of patients with or without amiodarone treatment, adjusted for baseline variables. (Reproduced with permission from *Br Heart J*,²³)

factors such as transient ischemia and sympathetic drive may be important in the balance of overall benefit/risk. The Cardiac Arrhythmia Suppression Trial shows that class IC agents have an overall adverse effect on benefit/risk. However, moricizine, based on preliminary Cardiac Arrhythmia Suppression Trial results, may not. Beta blockers, relatively poor antiectopic agents, nonetheless have antifibrillatory potential, decreasing the risk of ventricular fibrillation in animal models of acute ischemia.²⁸ Amiodarone also decreases sudden death in these models.²⁹ In other studies,³⁰ the combination of a class I drug (aprinidine) and coronary ligation (acute ischemia) increased malignant arrhythmia risk, but not drug alone. These data suggest clinical hypotheses for future testing.

FUTURE ANTIARRHYTHMIC STUDIES IN CONGESTIVE HEART FAILURE: A cooperative Veterans Administration study was begun in 1989 and will enroll 800 patients with CHF and arrhythmias, comparing outcome of amiodarone versus placebo therapy. The study end point is mortality (arrhythmic death/cardiac arrest). In addition to testing new agents (such as moricizine, amiodarone, sotalol), future trials should test other end points, such as electrophysiologic end points in patients with low ejection fraction and complex arrhythmias but without a prior sustained event.

OVERALL APPROACH TO ARRHYTHMIA THERAPY IN CONGESTIVE HEART FAILURE: A current treatment approach may be summarized as follows. Ventricular arrhythmias in CHF are prognostically important and indicate a need to consider preventive therapy. Reversible factors, such as ischemia, electrolyte imbalance and drugs or toxins, should be identified and treated. Therapy for CHF should be optimized, but electrolyte imbalance avoided. Converting enzyme inhibitors may decrease arrhythmias and mortality and should be considered early in therapy. Carefully titrated β blocker therapy may be considered in compensated (class II/III) postinfarction and (investigational) dilated cardiomyopathy patients. Antiarrhythmic drug therapy should be given to patients with a history of a sustained ventricular tachyarrhythmia and therapy guided by invasive and/or aggressive noninvasive testing. Symptomatic, frequent unsustained ventricular tachycardia, especially if ≥ 6 to 10 beats duration, also deserves consideration for therapy. Avoidance of class IC agents and use of electrophysiologic study, as well as noninvasive monitoring, should be encouraged in guiding such therapy. Antiarrhythmic agents should be selected after careful consideration of overall benefit/risk profile and response carefully monitored. For selected patients in whom an optimal antiarrhythmic drug regimen is not found, an automatic cardioverter-defibrillator device or, rarely, cardiac transplantation may provide effective therapy.

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Should Asymptomatic Ventricular Arrhythmia in Patients with Congestive Heart Failure Be Treated? An Antagonist's Viewpoint

Philip J. Podrid, MD, and John S. Wilson, MD

The importance of ventricular arrhythmia is based on its association with sudden cardiac death. It has become increasingly recognized that in some groups of patients (e.g. those with a recent myocardial infarction) the presence of runs of nonsustained ventricular tachycardia significantly increases the risk for a malignant ventricular tachyarrhythmia and sudden cardiac death.^{1,2} A similar association has been reported in patients with a cardiomyopathy and congestive heart failure (CHF), but data are conflicting.^{3,4} More importantly, the role of antiarrhythmic drug therapy for prevention of sudden death has not been established. This paper reviews the prognostic importance of repetitive ventricular arrhythmia and the benefits and hazards of antiarrhythmic drugs in such patients, concluding that routine therapy for such patients is of no proven benefit.

Prevalence of arrhythmia and sudden cardiac death in patients with cardiomyopathy and congestive heart failure: Ventricular premature beats are particularly frequent in patients with a cardiomyopathy and CHF (Table I). Frequent ventricular premature beats occur in 70 to 95% of patients with cardiomyopathy of any etiology while runs of nonsustained ventricular tachycardia are documented in 40 to 80%. Their frequency and complexity are not closely associated with the degree of left ventricular impairment. There are many factors that predispose to ventricular arrhythmia in such patients (Table II).

Structural factors resulting from the underlying cardiac pathology provide the appropriate substrate. As a result of myocardial damage, reentrant circuits capable of generating and sustaining arrhythmia may exist within the abnormal myocardium.

Electrolyte depletion, most often diuretic-induced hypokalemia or low magnesium, is an important factor that can alter membrane excitability and automaticity.

Hemodynamic factors, including ischemia, left ventricular dysfunction, contraction abnormalities, stretch on the myocardium and increased intracardiac pressure can induce ventricular arrhythmia.

Neurohormonal mechanisms, particularly activation of the sympathetic nervous and renin-angiotensin sys-

tems, can interact with an unstable myocardium and precipitate arrhythmia.

The drugs used for treatment of CHF, including digoxin, positive inotropic agents, β agonists and perhaps vasodilators, can induce or aggravate arrhythmia.

A number of studies have reported a high yearly mortality in patients with a congestive cardiomyopathy, regardless of the etiology (Table III). It had been assumed that the cause of death in patients with a cardiomyopathy is progressive CHF. However, it has become apparent that a significant proportion of the deaths are sudden, the result of a sustained ventricular tachyarrhythmia (Table III). While a bradyarrhythmia has been observed to be the mechanism in a few patients, in the vast majority the etiology is a sustained ventricular tachyarrhythmia. The proportion of death that is sudden is unrelated to the nature of the underlying heart disease.

Relation between arrhythmia and sudden cardiac death: In patients with a cardiomyopathy and CHF, the relation between nonsustained ventricular tachycardia and an increased risk of sudden cardiac death continues to be controversial as data from the reported studies are conflicting (Table IV).

Each of the trials involving patients with a recent myocardial infarction has reported that nonsustained ventricular tachycardia is an independent risk factor for sudden cardiac death, increasing mortality irrespective of left ventricular function, which is another independent factor (Table V). The highest mortality, however, is in those patients who have both nonsustained ventricular tachycardia and ventricular dysfunction (Table VI).

In conclusion, runs of nonsustained ventricular tachycardia are associated with an increased risk of sudden death in patients with a recent myocardial infarction who have left ventricular dysfunction or CHF. The relation between this arrhythmia and sudden death in patients with an idiopathic-dilated cardiomyopathy remains uncertain, although most of the studies that involve a larger number of patients have reported a significant association.

Role of electrophysiologic testing in predicting the patient at risk: Electrophysiologic testing is an important and useful technique for evaluating arrhythmia mechanism and establishing drug efficacy in patients with sustained tachyarrhythmias. The role of electrophysiologic testing for establishing risk in the patient with a cardiomyopathy and CHF who has nonsustained ventricular tachycardia remains uncertain, controversial

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TABLE I Prevalence of Ventricular Arrhythmia in Patients with Congestive Heart Failure

Study	n	% with VPB or Couplets	% with NS/T
Huang ⁴	35	93	60
Wilson [*]	77	71	50
Meinertz ³	74	87	49
Maskin [†]	35	92	71
Von Olshausen [‡]	60	95	80
Holmes [§]	31	87	39
Chakko ¹⁴	43	88	51
Francis	346	81	28
Unverferth ¹⁵	69	NA	41
Costanzo Nordin [*]	55	76	40
Neri ¹⁷	65	95	80
Overall	890	78	45

* JACC 1983;2:403; [†] Am Heart J 1984;107:896; [‡] Br Heart J 1984;61:955; [§] Am J Cardiol 1985;55:146; ^{||} Am J Cardiol 1986;57:38; ^{*} Cathet Cardiovasc Diagn 1985;11:445.

NA = not available; NSVT = nonsustained ventricular tachycardia; VPB = ventricular premature beats.

TABLE II Factors Predisposing to Arrhythmia in Patients with Congestive Heart Failure

Underlying structural disease—abnormal substrate
Electrolyte abnormalities
Potassium
Magnesium
Hemodynamic abnormalities
LV dysfunction and contraction abnormalities
Stretch on myocardium—increased ventricular volume
Increased ventricular pressure
Ischemia
Neurohormonal changes
Renin angiotensin
Sympathetic nervous system
Therapeutic interventions
Digoxin
Diuretics
β agonists
Phosphodiesterase inhibitors
Vasodilators
ACE inhibitors

ACE = angiotensin-converting enzyme; LV = left ventricular.

and investigational as data are conflicting (Table VII). The number of patients involved is small and protocols and endpoints have varied. Moreover, the patients with a decreased ejection fraction, but no clinical CHF, are often included.

Effect of treatment of congestive heart failure on ventricular arrhythmia and survival: Given the high incidence of sudden cardiac death in patients with a cardiomyopathy and CHF, an important question is whether treatment of CHF can decrease the frequency of ventricular arrhythmia and sudden death mortality. Some of these agents have been shown to decrease death from CHF. However, data about their role for suppressing ventricular arrhythmia and preventing sudden death are sparse and disappointing. A few studies evaluating the effects of direct-acting vasodilators on symptoms or survival reported the effect of this treatment on arrhythmia (Table VIII). No benefit from isosorbide dinitrate⁵ or hydralazine⁶ was observed, while

with minoxidil,⁷ there was a trend toward increased arrhythmia. While the impact of phosphodiesterase inhibitors (amrinone and milrinone) on survival has not been adequately studied, these positive inotropic agents may have an adverse effect on ventricular arrhythmia.⁸ The orally active β agonists have an uncertain effect on survival and may provoke arrhythmias.⁹ Diuretics may also play an important role in arrhythmogenesis due to electrolyte depletion, especially hypokalemia and low magnesium, which are factors known to increase the frequency of ventricular arrhythmia in patients with heart disease. Angiotensin-converting enzyme inhibitors decrease mortality from CHF and there have been interesting findings with respect to their effect on ventricular arrhythmias. Captopril does decrease ventricular arrhythmia, although enalapril is of less benefit,^{10,11} suggesting that this effect is independent of inhibition of angiotensin II. These studies, however, did not report mortality data.

TABLE III Total Cardiac Mortality and Sudden Cardiac Death in Patients with Congestive Heart Failure

Study	n	Follow-Up (mos)	Total Deaths (%)	Sudden Death	(%) Sudden Death
Francis [*]	159	20	73 (46)	46	(63)
Huang ⁴	35	34	4 (11)	2	(50)
Sakurai [†]	190	NA	87 (46)	19	(22)
Wilson [‡]	77	12	77 (100)	19	(25)
Meinertz ³	74	11	19 (26)	12	(63)
Maskin [§]	35	NA	25 (71)	1	(4)
Von Olshausen	60	12	7 (12)	3	(43)
Holmes [§]	43	14	14 (33)	12	(86)
Chakko ¹⁴	43	16	16 (37)	10	(62)
Franciosa ^{**}	182	12	88 (48)	40	(45)
Massie ^{††}	56	13	29 (52)	13	(34)
Lee ^{‡‡}	178	36	155 (76)	57	(37)
Burggraf ^{§§}	28	60	17 (61)	9	(53)
Cohn	106	1-62	60 (57)	28	(47)
Overall	1,266		671 (52)	271	41

* Am J Cardiol 1986;57:38; [†] Jap Card J 1983;47:581; [‡] JACC 1983;2:403; [§] Am Heart J 1984;107:896; ^{||} Br Heart J 1984;51:995; ^{*} Am J Cardiol 1985;55:146; ^{**} Am J Cardiol 1983;51:831; ^{††} Circulation 1981;63:269; ^{‡‡} Circulation 1984;70(suppl 1):II-113; ^{§§} Circulation 1975;51:146; ^{||} N Engl J Med 1984;311:819.

NA = not available.

TABLE IV Relation Between Ventricular Ectopic Activity and Sudden Cardiac Death in Patients with Congestive Heart Failure

Study	n	Follow-Up (mos)	Relation of VEA to SCD
Huang ⁴	35	34	0
Wilson*	77	12	0
Meinertz ³	74	11	+
Von Olshausen ⁷	60	12	0
Holmes ²	43	14	+
Chakko ¹⁴	43	16	+
Unverferth ¹⁵	61	12	+
Costanzo-Nordin ⁵	55	16	0
Follansbee ¹	19	19	+
Gradman ⁵	295	16	+

* JACC 1983;2:403; ¹ Br Heart J. 1984;51:995; ² Am J Cardiol 1985;55:146; ³ Cathet Cardiovasc Diagn 1985;11:445; ⁴ Am J Med 1980;92:741; ⁵ JACC 1989;14:564.
SCD = sudden cardiac death; VEA = ventricular ectopic activity.

TABLE V Ventricular Arrhythmia After Myocardial Infarction

Study	n	Duration of Monitoring (hrs)	Follow-Up (mos)	Sudden Death (%)	
				No Complex VEA	Complex VEA
Bigger ¹	820	24	12	12	36
Kotler*	160	6	36	20	60
Moss ¹	978	6	36	4	15
Mukharji ²	388	24	14	3	16
Rappaport ³	139	24	12	6	34
Ruberman ⁵	1,739	1	42	8	25
Vismara ¹	64	10	26	11	30
Schultz ¹	81	24	7	0	28

* Circulation 1973;47:959; ¹ Circulation 1979;60:958; ² JACC 1983;1:391; ³ N Engl J Med 1977;297:750; ⁴ Am J Med 1975;59:6; ⁵ Am J Med 1977;62:192.
VEA = ventricular ectopic activity.

TABLE VI Percent Sudden Death at 1 Year

	No Complex VEA		Complex VEA	
	LV Intact	LV Dysfunction	LV Intact	LV Dysfunction
Bigger ¹	6	22	12	35
Mukharji ²	2	7	7	25
Ruberman*	3	7	12	22
Schultz ¹	0	0	0	28

* N Engl J Med 1977;297:750; ¹ Am J Med 1977;62:192.
LV = left ventricular; VEA = ventricular ectopic activity.

The effect of treatment for CHF on outcome has now been reported by several large multicenter studies. In the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), enalapril decreased mortality by 27% compared to placebo.¹² However, the decrease was entirely due to a reduction in death from progressive CHF. The largest trial to date evaluating the effect of CHF therapy on mortality is the Veterans Administration Cooperative Study on Vasodilator Therapy of Heart Failure¹³ involving placebo, hydralazine or prazosin. Those receiving hydralazine and nitrate therapy, but not the prazosin group, had a 28% decrease in mortality compared to placebo. However, no specific

TABLE VII Predictive Accuracy of Electrophysiologic Studies in Patients with Cardiomyopathy and Nonsustained Ventricular Tachycardia

Study	No. with Cardiomyopathy	No. Inducible	Follow-Up (mos)	Predictive
Veltri*	6	3	23	0
Sulpizi ⁷	9	5	29	0
Das ²	24	8	12	0
Poll ⁵	20	1	18	0
Gomes ¹	10	?	30	+
Zheutlin ¹	13	7	22	++
Buxton**	18	9	33	0

* Am J Cardiol 1985;56:303; ¹ Am J Cardiol 1987;59:841; ² Am J Cardiol 1986;58:999; ³ Am J Cardiol 1986;58:992; ⁴ Circulation 1984;70:43; ⁵ Am Heart J 1986;111:850; ⁶ Am J Cardiol 1984;53:1275.
* Only noninducibility predictive.

TABLE VIII Treatment of Congestive Heart Failure—Effect on Ventricular Arrhythmia

Study	Drug	n	Effect on Arrhythmia
Franciosa ⁵	Isosorbide dinitrate	32	0
Franciosa ⁶	Hydralazine	32	0
Franciosa ⁷	Minoxidil	17	↑
Packer*	Amrinone	103	↑
Anderson ¹	Milrinone	12	↑
Ferrick ¹	Milrinone	33	↑
Holmes ⁵	Milrinone	15	~
DiBianco ⁸	Milrinone	230	↑
Ludmer ¹	Milrinone	74	0
Sharma ⁹	Pirbuterol	14	↑
Mettauer ¹	Salbutamol	20	↑
Cleland ¹⁰	Captopril	14	↓
Captopril-Digoxin Multicenter Group**	Captopril	300	↓
Cleland ¹¹	Enalapril	20	0-↓
Webster ¹¹	Enalapril	19	↓

* Circulation 1984;70:1038; ¹ Am Heart J 1986;111:461; ² Circulation 1986;74(suppl II):II-508; ³ Circulation 1984;70(suppl II):II-11; ⁴ Am J Cardiol 1987;59:1351; ⁵ Am Heart J 1985;104:840; ⁶ JAMA 1988;259:539; ⁷ Am J Cardiol 1985;56:566.
VPBs = ventricular premature beats.

analysis was performed to establish the cause of death or the impact of therapy on the occurrence of ventricular arrhythmia.

In conclusion, some direct-acting vasodilators and angiotensin-converting enzyme inhibitors have been shown to decrease symptoms from CHF and improve quality of life. Their effect on ventricular arrhythmia is variable but probably clinically unimportant. While they have been shown to improve survival by decreasing the mortality due to CHF, they have not been shown to affect sudden death mortality.

Role of antiarrhythmic drug therapy in preventing sudden death in patients with a cardiomyopathy and congestive heart failure: The association between sudden death and ventricular arrhythmia remains uncertain and controversial and the role of antiarrhythmic drugs for suppressing nonsustained ventricular tachycardia and preventing sudden death in patients with a cardiomyopathy and CHF remains unknown as there are only a few studies. Chakko and Gheorghiad¹⁴ ran-

TABLE IX Randomized Trials of Antiarrhythmic Drugs In Patients Post Myocardial Infarction

Study	Drug	n	Duration of Therapy	% Mortality or Sudden Cardiac Death		p Value
				Placebo	Drug	
Morgensen*	Lidocaine	79	days	11.0	12.0	NS
Bennett†	Lidocaine	610	days	7.0	16.0	NS
Lie‡	Lidocaine	212	days	10.8	0	<0.05
Ryden§	Tocainide	112	6 months	8.9	8.9	NS
Campbell	Mexiletine	97	4 yrs	1.8	2.3	NS
Chamberlain†	Mexiletine	344	1 yr	11.6	13.2	NS
IMPACT**	Mexiletine	630	1 yr	4.8	7.6	NS
Hugenholtz††	Aprindine	193	1 yr	9.3	7.3	NS
Gottlieb‡‡	Aprindine	143	1 yr	22.2	17.8	NS
Jones§§	Quinidine	103	3 days	12.4	8.9	NS
Holmberg	Quinidine	104	15 days	7.2	10.7	NS
Jennings†††	Disopyramide	95	1 yr	10.2	4.0	NS
Zainel***	Disopyramide	60	3 weeks	26.7	3.3	<0.05
Koch Weser††††	Procainamide	70	3 weeks	6.1	0	<0.05
Kosowsky‡‡‡	Procainamide	78	1 yr	10.3	3.7	<0.05
Collaborative§§§	Phenytoin	560	1 yr	11.0	9.4	NS
Peter	Phenytoin	150	2 yrs	18.0	24.0	NS
CAST***	Encainide	1,455	10 months	3.0	7.7	<0.001
	Flecainide					

* *Acta Med Scand Suppl* 1970;513:1; † *Lancet* 1970;2:909; ‡ *N Engl J Med* 1974;291:1324; § *Am Heart J* 1980;100:1006; || *J Cardiovasc Pharmacol* 1979;1:43; †† *Lancet* 1980;2:1224; ** *JACC* 1983;4:1148; ††† *Management of VT: Role of Mexiletine* In Sandoe E, Julian DG, Bell JW (eds). 1978: 572; †††† *Circulation* 1987; 75:792; ††††† *Am J Cardiol* 1974; 33:655; †††††† *Acta Med Scand* 1967; 181:297; ††††††† *Lancet* 1976;1:51; †††††††† *Lancet* 1977;2:88; ††††††††† *N Engl J Med* 1969;281:1253; †††††††††† *Circulation* 1973;47:1204; ††††††††††† *Lancet* 1971;2:1055; †††††††††††† *Br Heart J* 1978;42:135; ††††††††††††† *N Engl J Med* 1989;321:406.

domized 23 patients with a cardiomyopathy and ventricular arrhythmia to therapy with either procainamide or quinidine while 20 patients did not receive antiarrhythmic therapy. During the follow-up, there were 16 deaths, 10 of which were sudden; this was independent of therapy. However, the role of antiarrhythmic drugs is uncertain because therapy was not guided by arrhythmia suppression. In the report of Unverferth et al.¹⁵ 24 of 69 patients were treated with antiarrhythmic drugs. The 1-year mortality was not affected by drug therapy. However, as with the previous study, no conclusions are possible as data about the effect of these drugs on the suppression of arrhythmia are not supplied. Parmley and Chatterjee¹⁶ reviewed the outcome of 26 patients with CHF and complex arrhythmia who were treated with procainamide, quinidine or amiodarone. This was not a randomized study and the effect of the drugs on arrhythmia frequency is not commented upon. However, sudden death mortality was decreased in patients receiving antiarrhythmic drugs. Neri et al.¹⁷ reported on 41 patients with a dilated cardiomyopathy who were treated with amiodarone. The drug significantly decreased the frequency and complexity of ventricular arrhythmia as well as sudden deaths (0 versus 4 on placebo). While it appears that those with nonsustained ventricular tachycardia are at an increased risk for sudden death, it is unclear if the suppression of such arrhythmia by antiarrhythmic drugs will prevent this outcome.

The role of antiarrhythmic drugs in patients with nonsustained ventricular tachycardia and left ventricular dysfunction after a myocardial infarction is also of unproven benefit. A number of randomized antiarrhythmic drug studies in such patients have not reported a decrease in mortality (Table IX). However, none were

designed as arrhythmia suppression trials and for this reason the National Institutes of Health initiated the Cardiac Arrhythmia Suppression Trial (CAST). A recent report from the CAST investigators indicated that there was an increase in arrhythmic mortality in patients treated with encainide and flecainide compared to placebo.¹⁸ The role of antiarrhythmic drugs in the post-infarction patient is therefore still unknown, although the CAST results suggest that these agents are of no benefit and may indeed be harmful.

In contrast to the studies of antiarrhythmic drugs, a number of randomized postmyocardial infarction β -blocker trials have reported a decrease in sudden death (Table X). Most of the studies do not separately analyze the outcome of patients with decreased left ventricular function and the effect of β blocker on ventricular arrhythmia was not systematically evaluated. However, in a subgroup analysis of the β -Blocker Heart Attack Trial (β HAT), Furberg et al.¹⁹ reported that the difference in mortality between the placebo and propranolol-treated groups was more pronounced in patients with decreased left ventricular function. In another analysis of the β HAT data, Chadda et al.²⁰ reported a 47% decrease in sudden death among the propranolol-treated patients who had CHF complicating the myocardial infarction compared to only a 13% decrease in sudden death among the propranolol-treated patients without CHF.

Beta blockers have also been used in patients with cardiomyopathy. Anderson et al.²¹ randomly assigned 50 patients with CHF to receive standard therapy alone or with metoprolol. While there was no difference in outcome between the groups when analyzed by intention to treat, there was a favorable trend in survival in the

TABLE X Randomized Trials of β Blockers in Patients After a Myocardial Infarction

Study	Drug	n	Duration of Therapy	% Mortality or Sudden Cardiac Death		p Value
				Placebo	Drug	
Snow, Manc*	Propranolol	101	28 days	12.0	6.0	<0.03
Multicenter†	Propranolol	195	28 days	9.3	7.1	NS
Balcon‡	Propranolol	114	28 days	10.5	12.3	NS
Norris§	Propranolol	454	3 weeks	7.5	8.8	NS
β HAT	Propranolol	3,857	2 yrs	9.8	7.2	<0.01
Norwegian¶	Propranolol	560	1 yr	8.2	4.0	0.038
Wilhelmsen**	Alprenolol	230	2 yrs	9.6	2.6	<0.05
Ahlmark††	Alprenolol	162	1 yr	11.1	1.2	<0.05
Anderson‡‡	Alprenolol	282	1 yr	20.6	9.2	<0.01
Multicenter§§	Practolol	3,038	1 yr	3.6	2.0	<0.01
Hjalmarsson	Metoprolol	1,395	90 days	8.9	5.7	<0.03
Norwegian¶¶	Timolol	1,884	33 months	13.9	7.7	<0.001
Julian***	Sotalol	1,456	1 yr	8.9	7.3	NS
Taylor†††	Oxprenolol	1,103	6 yrs	9.3	8.2	NS

* Lancet 1965;2:551; † Lancet 1966;2:1435; ‡ Lancet 1966;2:917; § Br Med J 1968;2:398; || JAMA 1982;247:1707; ¶ Br Med J 1982;284:155; ** Lancet 1974;2:1157; †† Lancet 1974;1:1563; ‡‡ Lancet 1974;2:865; §§ Br Med J 1977;2:419; ||| Lancet 1981;2:823; ¶¶ N Engl J Med 1981;304:801; *** Lancet 1982;1:1142; ††† N Engl J Med 1982;307:1293.

group receiving metoprolol when analyzed for actual treatment received. Swedberg et al²² reported a significant increase in survival in 24 patients treated with metoprolol, but there was no comparative placebo group, only historical control subjects. Unfortunately, neither of these studies addressed the effect of β blockade on ventricular arrhythmia. Beta blockers are the only class of drugs shown to have an effect on sudden death in patients with CHF due to an acute myocardial infarction or a cardiomyopathy.

Limitations of antiarrhythmic drug therapy in patients with congestive heart failure: The use of antiarrhythmic drug therapy in patients with clinically significant CHF is limited by a low rate of efficacy and an increased risk of drug-induced toxicity. Hohnloser et al²³ reported that left ventricular ejection fraction was an independent predictor of drug efficacy and long-term outcome on drug. When the ejection fraction was <35% (mean 24), drugs were effective in only 34% of trials, while the efficacy rate was 46% when the ejection fraction was >35% ($p = 0.03$). The ejection fraction was significantly lower (29%) in patients without successful pharmacologic control of arrhythmia compared to those in whom arrhythmia was suppressed (42%, $p = 0.017$). During long-term follow-up, patients with recurrent arrhythmia had a left ventricular ejection fraction of 31% compared to 44% in those free of arrhythmia recurrence. Pratt et al²⁴ reported on 50 patients receiving ethmozine in whom the average ejection fraction was lower (29%) when drug therapy was discontinued because of inefficacy when compared to the ejection fraction of those continuing drug therapy (40%, $p < 0.01$). Similar results were reported by Hession et al²⁵ who observed that 35% of patients with a left ventricular ejection fraction >40% responded to ethmozine compared to an 18% response rate when the ejection fraction was <40%. In a study of tocainide in 228 patients, Hohnloser et al²⁶ reported that the ejection fraction was lower in nonresponders (37 vs 43%). Tordjman et al²⁷

reported on encainide in 102 patients and in those with an ejection fraction >35%; the response rate was 50% while only 29% of those with a value of <35% responded to the drug ($p < 0.03$).

Another problem is that in the presence of CHF, drug pharmacokinetics are significantly altered, initially affecting blood levels which in turn affect dose requirements.²⁸ The plasma concentration of the drug is related to its volume of distribution and, when decreased, as occurs in CHF, a result of a reduction in tissue perfusion, the plasma concentration of the drug is greater.²⁸ In CHF, the decreased tissue perfusion also causes changes in distribution, metabolism and clearance of the antiarrhythmic agents, a result of a decrease in blood flow to the kidneys and liver. Additionally, there is a decrease in hepatic metabolic enzyme activity. As a result, the metabolism and clearance of these agents are impaired, causing an increase in the elimination half-time.²⁸ Also, the time required to reach a steady blood level state at any given dose of drug administered is increased and the dose of the antiarrhythmic drug administered to those with CHF should be decreased and the upward dose titration carried out very slowly and cautiously in order to avoid excessive blood levels and toxicity.

Patients with CHF usually receive a number of other cardioactive drugs, especially digoxin, and drug-drug interactions have been reported.²⁸ Diuretic drugs are usually prescribed to patients with CHF and the incidence of diuretic-induced hypokalemia and low magnesium is substantial; this may be responsible for the provocation of sustained ventricular arrhythmias in vulnerable patients who have underlying myocardial disease and poor left ventricular function.²⁹ Additionally, hypokalemia may interfere with and negate antiarrhythmic drug activity by enhancing membrane automaticity and excitability and decreasing the refractory period.³⁰ Hypokalemia and perhaps low magnesium may be associated with an increased risk of antiarrhythmic drug-in-

duced arrhythmia aggravation, especially the precipitation of torsade des pointes.³¹

Aggravation of arrhythmia is a serious complication caused by each of the antiarrhythmic drugs.³² This has been defined as an exacerbation of a preexisting arrhythmia or the provocation of new arrhythmia for the patient. The overall incidence is 9% when noninvasive methods are used while the incidence is 18% when electrophysiologic testing is used. The only factors associated with an increased risk of arrhythmia aggravation are the nature of the presenting arrhythmia and presence of left ventricular dysfunction and CHF.³² The average ejection fraction in patients who experienced arrhythmia aggravation was lower (37%) compared to the value in those without this complication (43%, $p = 0.08$). However, patients with an ejection fraction $<35\%$ and a history of CHF had a greater risk (odds ratio 2.2) for experiencing this complication compared to those in whom the ejection fraction was $>35\%$ ($p = 0.04$).

Another important and serious cardiac complication of antiarrhythmic drugs is the precipitation or exacerbation of CHF. In a retrospective review of 100 patients receiving therapy with disopyramide, Podrid et al³³ reported that 55% of patients with a history of CHF had an exacerbation of CHF while this complication developed in 5% of those without a previous history of left ventricular decompensation. In a retrospective review of their experience with the newer antiarrhythmic drugs, Ravid et al³⁴ reported a 1.9% overall incidence of CHF exacerbation. However, among those with a medical history of CHF, the incidence was 3.8%. All but 1 patient who experienced this complication had a history of CHF. The only predictors of an increased risk of drug-induced CHF were a clinical history of CHF, a cardiomyopathy and an ejection fraction $<35\%$.

While most studies have reported that serious cardiac complications occur primarily in patients with advanced heart disease, clinical CHF and markedly decreased left ventricular function, the recently reported results of CAST are disturbing.¹⁸ This trial involved patients with asymptomatic ventricular arrhythmia after a myocardial infarction who had mild-to-moderate left ventricular dysfunction but no overt clinical CHF. Patients were randomized to receive encainide, flecainide, moricizine (ethmozine) or placebo with therapy based on suppression of arrhythmia. After a 10-month follow-up, there was an excessive total number of cardiac and sudden deaths in the patients receiving encainide or flecainide compared to placebo (56 vs 22 total deaths and 33 vs 9 sudden deaths). While the results of this study in postmyocardial infarction patients cannot be applied to other patient groups or other antiarrhythmic drugs, it does highlight the potential hazards of the antiarrhythmic drugs even in a healthier group of patients. This provides even further concerns about the use of antiarrhythmic therapy in sicker patients with CHF who have asymptomatic arrhythmia. While such patients may be at an increased risk of sudden death, there are no data that these drugs are of benefit, but may be potentially hazardous in this patient group. Given this unfavorable

risk-benefit ratio, antiarrhythmic drug therapy should not routinely be administered to patients with a cardiomyopathy and CHF who have asymptomatic ventricular arrhythmia.

In conclusion, while asymptomatic nonsustained ventricular tachycardia may identify the patient with CHF who is at increased risk for sudden death, the data are contradictory. It is unproven if suppression of this arrhythmia will prevent sudden death. Given the relatively low efficacy of the antiarrhythmic drugs in patients with CHF, the increased risk of cardiac toxicity, especially arrhythmia aggravation in such patients, and the potential for increased mortality, routine treatment of asymptomatic ventricular arrhythmia in these patients is not justified until such time as there are better methods for identifying the individual patient at risk. Each patient should be considered individually with attention paid to the benefit-risk ratio.

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Are Nitrates Effective in the Treatment of Chronic Heart Failure? Antagonist's Viewpoint

Milton Packer, MD

Why shouldn't the truth be stranger than fiction?
Fiction, after all, has to make sense.

—Mark Twain

At first glance, nitrates would appear to be a rational approach to the treatment of chronic congestive heart failure (CHF). Nitrates act to attenuate the peripheral vasoconstriction that contributes to the hemodynamic derangements in this disorder; as a result, these drugs consistently improve cardiac performance when administered alone or in combination with other vasodilators. In addition, nitrates act as coronary vasodilators to improve myocardial blood flow; this effect may be particularly important in CHF, since ischemia may play a role in the progression of left ventricular dysfunction. Even in the absence of an antiischemic effect, nitrates might reduce the long-term morbidity and mortality in this disorder, since these drugs can minimize the progressive ventricular enlargement that is characteristic of worsening CHF.¹ Finally, nitrates are well tolerated by most patients with chronic CHF; these drugs cause hypotension, renal insufficiency, tachycardia or fluid retention much less frequently than other vasodilators. Hence, it is not surprising that most physicians use nitrates in the treatment of this disease, although nearly always in combination with digitalis, diuretics and a converting-enzyme inhibitor.

The results of controlled clinical studies, however, have raised considerable doubts about the efficacy of nitrates in the treatment of chronic CHF. Such doubts are not new. Physicians have questioned the long-term efficacy of nitrate therapy for over 100 years.² At the turn of the century, nitroglycerin was widely used to reduce blood pressure in patients with systemic hypertension, until careful studies showed that the short-term hypotensive actions of nitroglycerin did not persist during prolonged therapy.^{2,3} Consequently, as more effective antihypertensive drugs were developed, the use of nitrates in the management of this disorder disappeared. During the next

50 years, nitrates were primarily used in the management of ischemic heart disease. However, although nitroglycerin could abort the acute anginal attack, many physicians doubted whether prophylactic therapy with long-acting preparations was efficacious.⁴ Initially, this lack of efficacy was attributed to the uncertain bioavailability of these drugs,⁵ but recent studies have shown that even the delivery of adequate quantities of nitrates into the systemic circulation (either continuously or at frequent intervals) does not prevent the onset of effort-induced angina.^{6,7} Clinical benefits are seen only when long nitrate-free intervals are incorporated into the dosing regimen,^{7,8} but such an approach produces intolerable headaches and is accompanied by a high risk of rebound ischemia during the nitrate-free intervals.⁸ Consequently, enthusiasm for the use of nitrates in ischemic heart disease has waned, especially as other effective drugs for this condition have been introduced.

Given the disappointing experience with nitrates in the treatment of hypertension and angina, can we expect nitrates to be effective in the treatment of chronic CHF? The first report on the usefulness of nitroglycerin in patients with CHF was published by Johnson et al⁹ in 1957. Since that time, nitrates have enjoyed wide acceptance by the medical community, largely based on the results of short-term (and uncontrolled) studies reporting dramatic benefits of treatment. Nitrates have been used largely because physicians believed that vasodilator therapy made sense, and (until recently) few other vasodilators were available. Unfortunately, reasonable approaches to treatment do not always prove to be effective ones.

In this report we show that the doubts that have been raised about the efficacy of nitrates in the treatment of hypertension and exertional angina should also be raised with respect to their use in chronic CHF. We address 3 central questions: (1) Do nitrates produce long-term hemodynamic improvement? (2) Do nitrates produce long-term symptomatic benefits and enhance exercise tolerance? (3) Do nitrates reduce long-term mortality?

Do nitrates produce long-term hemodynamic improvement? A variety of nitrate preparations (nitroglycerin, isosorbide dinitrate, isosorbide mononitrate, erythritol tetranitrate and pentaerythritol tetranitrate) given by a variety of routes of administration (oral, sublingual, intravenous, transdermal and buccal) produce consistent short-term hemodynamic

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benefits in patients with chronic CHF, regardless of the cause of left ventricular dysfunction or the severity of symptoms. These short-term hemodynamic benefits are similar (and often superior) to the short-term effects of other vasodilator drugs (e.g., the converting-enzyme inhibitors),¹⁰ whose efficacy in the treatment of chronic CHF is established.

NITRATE TOLERANCE: There is considerable doubt, however, that the beneficial short-term effects of nitrates seen in patients with CHF can be sustained during long-term therapy. When given continuously (either transdermally or intravenously), the initial hemodynamic benefits of nitroglycerin are nearly completely lost after 24 to 48 hours of treatment.^{11,12} This tolerance can be prevented by the intermittent administration of nitroglycerin, but a nitrate-free interval of at least 8 to 12 hours is necessary to maintain responsiveness to the drug.^{13,14} Tolerance also develops to orally administered nitrates; the hemodynamic effects of oral isosorbide dinitrate become rapidly attenuated when doses are given every 4 or 6 hours, but not when the interdosing interval is increased to every 8 or 12 hours.^{15,16} These observations in patients with CHF are strikingly similar to those reported in patients with angina.⁷

At first glance, these results would appear to contradict the conclusions reached in 2 placebo-controlled trials, which reported sustained hemodynamic effects during long-term treatment with oral isosorbide dinitrate, even though the drug was administered 4 times daily.^{17,18} Both studies, however, evaluated only the first of the 4 daily doses of the drug, and this dose was usually administered in the morning after the patient had received no nitrates since the previous evening—a nitrate-free interval of about 10 to 12 hours. The second, third and fourth doses (which were given at intervals of 4 to 6 hours) were never evaluated. Moreover, because hemodynamic measurements require intravascular instrumentation, the need to perform invasive procedures on the morning of the hemodynamic study invariably delays the administration of the dose of isosorbide dinitrate to be tested; this may further prolong the nitrate-free interval (up to 14 hours¹⁷). Such delays may be long enough to restore nitrate responsiveness in patients who had developed tolerance to their dosing regimen. Even these long intervals, however, may not completely reverse the development of tolerance.¹⁸

There is now compelling evidence that the development of tolerance can limit the use of nitrate therapy in the treatment of chronic CHF. Although twice-daily (and perhaps 3-times-daily) dosing may maintain hemodynamic responsiveness, these dosing regimens have not been evaluated in controlled clinical trials.

Do nitrates produce long-term symptomatic benefits and enhance exercise tolerance? The only means of assessing the clinical efficacy of nitrates in the treatment of chronic CHF is to examine the data derived from well-designed, randomized, placebo-controlled trials. The results of uncontrolled studies

are always difficult to interpret, since both the symptoms and the exercise tolerance of patients with CHF can respond favorably to treatment with placebo.¹⁹ When the identity of a drug is known both to the patient and the physician, it is not infrequent for the drug being tested to be deemed effective, only for the reverse conclusion to be reached when the study is conducted under double-blind conditions. The challenge in any controlled clinical trial is to demonstrate that the improvement seen in patients receiving active therapy is greater than the improvement seen in patients treated with placebo (a "between-groups" analysis). All too often, however, the analysis focuses only on the statistical significance achieved in the actively treated group and ignores the changes produced by placebo (a "within-group" analysis). Such an approach is inappropriate, even if the changes in the placebo group are not statistically significant.

CONTROLLED CLINICAL TRIALS: Five controlled trials have investigated the long-term efficacy of nitrates in the treatment of chronic CHF.^{17,18,20-22} All 5 trials evaluated patients with class II and III CHF who were taking digoxin and diuretics, and all utilized a target dose of 40 mg of isosorbide dinitrate (or matching placebo) which was given 4 times daily. Four of the 5 trials evaluated only small numbers of patients (16 to 39 patients per study)^{17,18,20,21}; the fifth trial, although considerably larger, evaluated nitrates only in combination with hydralazine.²²

In 1978 Franciosa et al²⁰ reported the results of a placebo-controlled, crossover study in 16 patients with chronic CHF, in which isosorbide dinitrate and placebo was given to each patient for 8 weeks. Although exercise tolerance increased during oral nitrate therapy, a similar improvement was seen in patients treated with placebo, and there was no significant difference in the responses between the 2 groups. Symptoms tended to deteriorate during treatment with placebo, but these appeared to represent primarily the occurrence of rebound phenomena that were related to the abrupt withdrawal of previous nitrate therapy. Such rebound events, however, are most likely to occur in persons who have developed tolerance to the drug—in a fashion similar to the events seen after the abrupt withdrawal of narcotic analgesics.^{23,24} This observation (together with the lack of superiority over placebo with respect to exercise) suggests that isosorbide dinitrate was not an effective drug in this study.

In 1980 Franciosa et al¹⁷ reported the results of a placebo-controlled, parallel-design study in a second group of 16 patients with chronic CHF, who received either isosorbide dinitrate or placebo for 12 weeks. Overall, the 2 treatment groups showed similar clinical responses (4 patients in each group improved) and similar changes in the duration of tolerable exercise.²⁵ Although maximal oxygen consumption at peak exercise increased on isosorbide dinitrate, this was primarily due to an unusually marked response in 1 patient. Overall, the investigators concluded that

"clinical differences between placebo- and vasodilator-treated patients were not apparent."¹⁷

In a third controlled trial by Aranda et al,²¹ 30 patients with a congestive cardiomyopathy received either isosorbide dinitrate or placebo for 1 year, using a parallel-group design. There was no difference between the 2 treatment groups with respect to ventricular function or exercise tolerance after 3, 6, 9 or 12 months of therapy. These results are in striking contrast with the findings of another placebo-controlled study²⁶ (performed by the same group of investigators) which reported favorable effects of isosorbide dinitrate; in this latter study, however, the drug was given for only 2 weeks.

The most encouraging results with the use of nitrates in the treatment of CHF have been reported in a fourth trial (performed by Leier et al¹⁸), in which patients received either isosorbide dinitrate or placebo for 3 months. Exercise tolerance was prolonged to a greater extent in patients receiving nitrates compared with placebo; this difference was significant after only 1 and 2 months in one analysis²⁵ but only after 3 months in another.¹⁸ The functional status of nitrate-treated patients also tended to improve, although this effect was not significant. Unfortunately, interpretation of this study is complicated by the fact that during the course of the trial, deaths due to CHF occurred more frequently in patients treated with isosorbide dinitrate than in patients treated with placebo (4 vs 1); the exclusion of these patients from the final analyses may have influenced the conclusions of the study.

The largest study that has examined the efficacy of nitrates in the treatment of chronic CHF is the Veterans Administration Vasodilator Heart Failure Trial (V-HeFT), which randomly assigned 642 men to either placebo, prazosin, or a combination of isosorbide dinitrate and hydralazine for periods of 6 months to 5.7 years.²² Even when combined with hydralazine, isosorbide dinitrate did not enhance exercise capacity of treated patients after 2, 6, 18 and 24 months of therapy. The vasodilator combination increased exercise tolerance (compared with placebo) only at one time during the course of follow-up (after 12 months, $p = .02$), but this difference was no longer significant when adjustments were made for multiple tests over time. Interpretation of these data is further complicated by the fact that half of the patients were not taking their target doses of isosorbide dinitrate (or hydralazine) after 6 months because of a high incidence of adverse reactions.²⁷

We must conclude that, although some encouraging trends are apparent, the data from these 5 controlled trials (taken together) do not support the conclusion that nitrates are an effective approach to the treatment of chronic CHF.

Do nitrates reduce mortality in chronic heart failure? No study has evaluated the effect of long-term treatment with nitrates (when used alone) on the survival of patients with chronic CHF. In the V-HeFT

study, a combination of isosorbide dinitrate and hydralazine appeared to reduce mortality when compared with placebo, the difference between the groups being of borderline significance ($p = 0.09$).²⁷ Was this favorable trend related to treatment with isosorbide dinitrate, to hydralazine or to the combination? Many physicians have attributed the benefits seen in V-HeFT to the use of isosorbide dinitrate alone, since nitrates may exert a favorable effect on mortality in other clinical settings.²⁸ Analysis of the mortality data in the V-HeFT study, however, fails to support this belief. In the V-HeFT trial, the improvement in survival was related to an improvement in the left ventricular ejection fraction; patients whose ejection fraction increased by at least 3% (regardless of treatment assignment) fared better than those whose ejection fraction showed little change or decreased.²⁹ Therefore, patients treated with isosorbide dinitrate and hydralazine presumably fared better in the V-HeFT study because the combination increased the ejection fraction more than placebo.²⁹ This observation confirms an earlier report by Unverferth et al,³⁰ who first noted that long-term treatment with the combination of hydralazine and isosorbide dinitrate improves systolic function (compared with placebo); most important, this hemodynamic benefit was associated with regression of myocardial cellular hypertrophy. In the Unverferth study, however, the improvement in systolic function and myocardial hypertrophy that was seen with the vasodilator combination was entirely related to treatment with hydralazine and was not seen with isosorbide dinitrate alone. These data suggest that any beneficial effect of vasodilator therapy seen in the V-HeFT study was more likely to be related to hydralazine than to treatment with nitrates. Therefore, the effect of nitrate monotherapy on the mortality of chronic CHF remains undefined.

Conclusions: The arguments presented in this report lead to a single conclusion: Few data are available to support the widespread belief that nitrates are effective drugs in the treatment of chronic CHF. At least in the doses and dosing regimens that have been utilized in controlled trials, therapy with nitrates does not produce predictable long-term hemodynamic or clinical benefits. Although mortality may be favorably affected when nitrates are combined with hydralazine, this benefit appears to be more closely related to the use of hydralazine than to the use of nitrates.

Can we therefore conclude that nitrates are worthless drugs in the treatment of CHF? No. Current studies are plagued by inherent flaws in design and interpretation; future trials (if better executed) may demonstrate a favorable effect of nitrates in these patients. Yet, the problem with nitrates lies not only in the design of studies but also with the drugs themselves. Tolerance is the inevitable result of any attempt to use nitrates to produce round-the-clock hemodynamic improvement. To the extent that such

a goal is important in improving the clinical status of patients with CHF, we will almost certainly need to turn to other vasodilator drugs.

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Future Perspectives in the Management of Congestive Heart Failure

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In 1976, Comroe and Dripps¹ opined that >60% of advances in cardiovascular medicine had their origins in the basic sciences. To a large extent, that is a self-evident truth because advances in medicine, other than those occurring entirely by serendipity, must occur within the limits of available biologic knowledge. Furthermore, Comroe and Dripps did not report on the proportion of work in the basic sciences that never had clinical application.

In the last decade, advances in technology (angioplasty, pacing), biochemistry (thrombolysis) and pharmacology (angiotensin-converting enzyme inhibitors, calcium antagonists, lipid-lowering drugs) have had a major impact on the treatment of cardiovascular diseases. In the context of congestive heart failure (CHF), understanding of the underlying physiology has changed, old drugs are being used in new ways, new drugs have been discovered and transplantation has emerged as an effective novel form of therapy. In an adjacent article, Katz has identified some of the more recent scientific advances in the understanding of CHF, including the application of molecular biology to cardiovascular disease. Not all these advances will lead to important changes in therapy and benefit to patients. For the clinician, the key question is whether such knowledge can be applied to clinical problems, or, put more bluntly, "so what?" The successful application of scientific advances to clinical problems is often just as difficult as the original elucidation of the basic science.

Definition of heart failure: Heart failure is a generic phrase that includes many clinical syndromes. Often, adjectives have been added to the term "heart failure" in order to convey useful information between doctors. Thus, there is forward and backward, right and left, high and low output, systolic and diastolic, acute, chronic, relapsing and congestive heart failure. In general, it is sufficient to consider only acute heart failure, circulatory collapse and chronic heart failure. This report is concerned with chronic heart failure.

Many definitions of heart failure have been put forward (Table I). Most have emphasized 1 or more physiologic or biochemical aspects of heart failure and have been concerned with the scientific understanding of the condition. Physicians, on the other hand, use the phrase to describe a clinical syndrome and convey information

between themselves. A practical definition is that heart failure is a clinical syndrome, caused by an abnormality of the heart and recognized by a characteristic pattern of hemodynamic renal, neural and hormonal responses.²

Causes of heart failure: Traditionally, once abnormalities of cardiac rhythm, valves or pericardium have been excluded, CHF is attributed to coronary artery disease or described as a cardiomyopathy. Cardiomyopathy is divided on descriptive grounds into dilated, hypertrophic and restrictive. The major division is between those patients with coronary artery disease and those with dilated cardiomyopathy.

This classification of CHF is too simple. Further subsetting of patients is likely to lead to specific groups of patients who will benefit from particular treatments. An alternative approach to the description of patients (Table II) is based on the work of Linzbach.³ The most common cause of CHF is a decrease of the muscle mass available to bring about contraction. This usually results from myocardial infarction. A second common cause is incoordinate contraction in the presence of coronary artery disease. The remaining causes of CHF can be considered as either being extracellular or cellular. In the past, the presumption has been that patients with CHF have a cellular abnormality of systolic contraction. It is possible that in many patients, CHF is due to alterations in the architecture of the heart, the shape of the ventricle, slippage of adjacent cells and embedding of cells in a network of fibrosis. There would not have to be any abnormality of the myocyte itself. Numerous cellular abnormalities have been described, including down-regulation of β receptors,^{4,5} decreased cyclic-adenosine monophosphate,⁶ increased Gi proteins,⁷ decreased myocardial catecholamines,⁸ loss or alteration of the contractile proteins, abnormal function of the sarcoplasmic reticulum, altered calcium homeostasis,⁹ changes in the cytoskeleton and disease of small vessels.¹⁰ Although a decrease in contractile strength would be expected, experiments on isolated muscle have not shown a decreased response to a high concentration of extracellular calcium (Table III).^{5,6,9,11} The nature of any systolic abnormality of the myocardium in CHF must be more complex. The rate of contraction has in 1 report been shown to be unaltered,¹¹ but diastolic abnormalities have been identified, notably a delay in relaxation of the myocardium.^{6,9}

The response of the body to CHF is similar regardless of the etiology of the CHF (Table IV).

Systolic or diastolic heart failure: Diastolic heart failure is not a new concept having been described rather elegantly over 65 years ago.¹² Henderson¹² wrote, "... the rate of relaxation of the heart ... is quite as

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TABLE I Definitions of Heart Failure

Physiologic or biochemical definitions

A condition in which the heart fails to discharge its contents adequately³⁰

A state in which the heart fails to maintain an adequate circulation for the needs of the body despite a satisfactory filling pressure³¹

A pathophysiologic state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues³²

... syndrome ... which arises when the heart is chronically unable to maintain an appropriate blood pressure without support³³

Practical definitions

A clinical syndrome caused by an abnormality of the heart and recognized by a characteristic pattern of hemodynamic, renal, neural and hormonal responses

Ventricular dysfunction with symptoms

Abnormal function of the heart causing a limitation of exercise capacity

TABLE II Underlying Causes of Chronic Heart Failure

Loss of muscle

Commonly due to myocardial infarction

Incoordinate contraction

Often associated with ischemic heart disease

Extracellular abnormality

Fibrosis, altered extracellular architecture

Change of shape and size of ventricle

Slippage of cells, fiber reorientation

Cellular abnormality

Diastolic dysfunction common with

Hypertrophy

Ischemia

Small hearts and tachycardia

Fibrosis

Systolic dysfunction

Downregulation of receptors (e.g., sympathetic)

Reduced cAMP

Diminished function of sarcoplasmic reticulum

Abnormality of contractile proteins

cAMP = cyclic adenosine monophosphate.

TABLE III Response of Human Failing Myocardium to Calcium and Isoprenaline

				Developed Tension (mN/mm ²)			
				n	Rest	Calcium	Isoprenaline
Gwathmey et al	1987	Normal	8	3.8	13.8	—	—
		Failure	5	3.9	11.0	—	—
Ginsburg et al	1983	Normal	4	25	30	169	—
		DCM	20	37	27	74	—
		IHD	16	58	74	119	—
Feldman et al	1987	Normal	5	1.4	11.8	10.0	—
		Failure	7	1.4	12.9	7.5	—
Bohm et al	1988	Normal	4	—	=9	—	—
		Failure	13	—	=6.5	—	—

DCM = dilated cardiomyopathy; IHD = ischemic heart disease.

TABLE IV Body Responses to Heart Failure

Altered structure of heart

Starling's mechanism

Activated neuroendocrine systems

Redistribution of blood flow and increased peripheral resistance

Desensitization to catecholamines; altered myocardial receptors

Altered contractile proteins and biochemical systems in heart muscle

Altered function, histology and biochemistry of skeletal muscle

truly have inadequate ventricular filling at end-diastole (measurement of ventricular volumes needed) that limits exercise capacity (measure on exercise).

Progression of heart failure: CHF is a common condition occurring in up to 1% of the general population. The prognosis is poor but varies with severity (Figure 1). In severe CHF, 50% of patients are dead within 6 months,¹⁴ whereas if all patients with heart failure are considered, 25% are dead within 1 year.^{15,16} Several trials have reported or are being undertaken to investigate whether treatment can increase longevity. The idea behind many of these trials is that CHF is a progressive illness due to continuing damage to the myocardium (Figures 2 and 3). A popular concept is that this continuing damage reflects an increased wall stress in the myocardium. In some animal models and in some patients, it may be that the natural history of CHF follows such an inevitable downward course (Figure 3). However, 2 alternative possibilities exist. In many patients with CHF, the progress of the disease may not be due to any decrease in the inherent function of the heart muscle itself, but to adaptive mechanisms within the body (Figure 2). Malfunction of the kidney may lead to increasing sodium and water retention, alteration of central hemodynamics and worsening of clinical CHF. Alternatively, it may be that patients with CHF progress in a stepwise fashion due to further ischemic events, repeated exposure to the initiating factor or even sudden death (Figure 3).

Ischemic syndromes: Atheromatous disease in the coronary arteries is the most common cause of CHF. This is usually explained by a decrease in the mass of myocardium available for contraction or incoordinate contractility. Recently, several other syndromes have

important ... as the systolic contraction ..." and "If an old man's heart relaxes slowly, his capacity for physical exertion is thus limited."

Diastolic heart failure occurs particularly in the context of hypertrophied muscle in the presence of a small ventricular cavity and a fast heart rate. This situation commonly exists in hypertrophic cardiomyopathy, hypertensive heart disease, after aortic valve surgery and in many patients with coronary artery disease. The abnormality is due to slow relaxation (active and passive) of the heart, so that at end-diastole, the left ventricular end-diastolic pressure is increased and filling of the ventricle is not complete. Diastole comprises a period of isovolumic relaxation, rapid filling, passive filling and atrial contraction. Many papers have been published in which diastolic heart failure is regarded as existing in those patients who have a normal ejection fraction at rest (indicating broadly that the heart size was normal) and in whom there is a decreased rapid filling of the ventricle.¹³ For the clinician, the problem remains as to which patients, whether with small or enlarged hearts,

been variously described as stunned, hibernating, mummified,¹⁷ stuttering¹⁸ or preconditioned¹⁹ (Table V). Many of these entities are rather similar to what used to be called "chronic ischemia." The implication is that improved perfusion of the myocardium would lead to clinical benefits. The biochemical basis for stunned, hibernating or mummified myocardium is not understood and the diagnosis in patients is difficult, if not impossible, to make.

Causes of symptoms and mechanisms of improvement: Most patients with CHF are initially treated with diuretics and sometimes digoxin. Simple clinical skills allow the physician to adjust the dose of diuretics so that the body fluid compartments are normalized.²⁰ Even then, patients may continue to complain of symptoms, notably shortness of breath and fatigue. The origin of these symptoms is uncertain.²¹ Certainly, symptoms are not related simply to increased left atrial pressure because peak oxygen consumption is not determined by the left ventricular end-diastolic pressure at the end of exercise, drugs that alter the left atrial pressure do not result in a short-term improvement in exer-

cise performance and different forms of exercise can give rise to different terminating symptoms, despite similar changes in left atrial pressure. There are 3 major determinants of symptoms. First, in patients with CHF, ventilation in the lung is increased for a given carbon dioxide production.²² Second, blood flow to exercising skeletal muscle is limited because of an increased resistance. The cause of this increased resistance is not understood. Third, there are functional,²³ histologic²³ and biochemical changes in the skeletal muscle itself. Again, the cause for these changes is not understood. Some of the changes in skeletal muscle may be related to repetitive ischemia and rest atrophy and some may be related to a response to the altered neural and hormonal stimulation in CHF. What is now emerging is that an increase in exercise capacity with drugs used for therapy in CHF is associated with an increase in blood flow and improvement in the abnormalities in skeletal muscle. Indeed, it may be a principle of treatment that no benefit will accrue to the patient who has already been treated with diuretics unless blood flow to exercise in skeletal muscle is augmented. The ability of skeletal muscle to

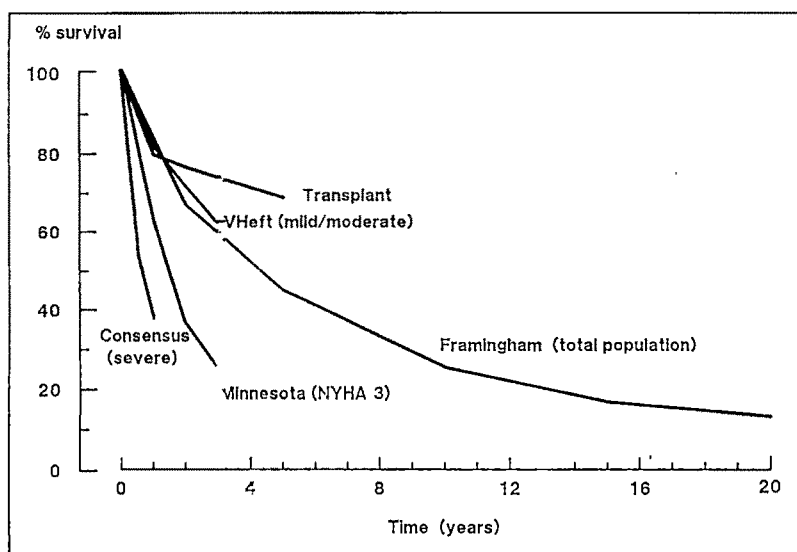


FIGURE 1. Prognosis of heart failure. NYHA = New York Heart Association; VHeft = Veterans Administration Heart Failure Trial.

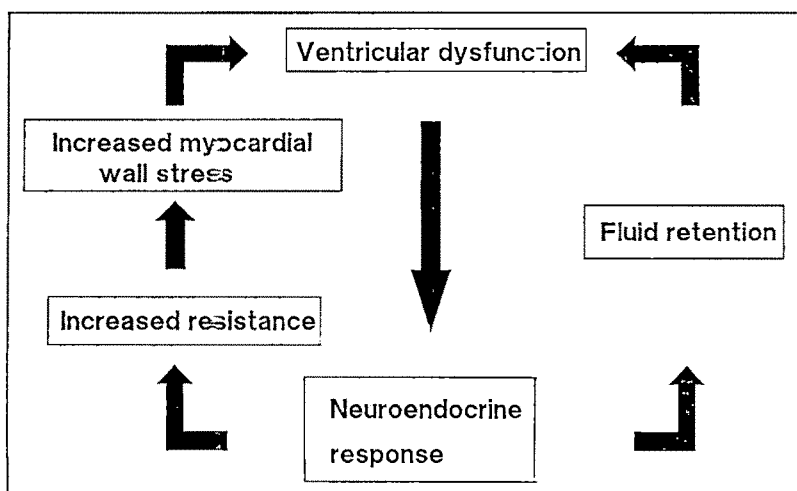


FIGURE 2. Spirals in heart failure. Left, progression of disease is determined by central hemodynamics and, in particular, wall stress in the myocardium. Right, progression of heart failure is due to retention of salt and water. Two different mechanisms are not mutually exclusive.

perform work under anaerobic conditions is extremely limited. Exercise capacity essentially depends on blood flow for the provision of oxygen.

Positive inotropic drugs: For years, physicians have believed that the major abnormality in CHF is a weakness of the systolic function of the heart. A consequence is the use of a positive inotropic drug for the treatment of such patients with chronic CHF. However, the evidence that such drugs are beneficial is poor.²⁴ There is a continuing controversy over the use of digoxin in patients in sinus rhythm. The case against digoxin is not that it is without effect, but that the benefit is small and less than can be achieved with other safer drugs. Digoxin is becoming redundant.

Numerous inotropic agents that have been studied in CHF have not been shown to be beneficial. This may be partly due to down-regulation of β receptors, the development of tolerance, exacerbation of arrhythmias or increasing damage to the myocardium.

A new principle is emerging, namely, that inotropic drugs in CHF may be harmful because they increase damage to the myocardium by increasing wall stress or myocardial ischemia. If that is true, then it has important implications for the development of new drugs. It is possible, however, that many inotropic drugs are harmful because they increase the cytosolic calcium concentration in myocytes causing arrhythmias and cell necrosis. There may be as yet undiscovered inotropic drugs that do not effect the calcium channel in the sarcoplasmic reticulum, but do increase contraction by altering the phosphorylation of the contractile proteins or some other mechanism. Such drugs would have selective intracellular effects and might be of benefit in subgroups of patients with CHF.

Vasodilators: Converting-enzyme inhibitors have been shown to be effective in decreasing symptoms, increasing exercise capacity and prolonging life¹⁴ in patients with CHF. The combinations of nitrates and hydralazine may also increase longevity.²⁰ A key question is the mechanism by which these effects are being brought about. Figure 4 contains a possible mechanism for the effect of angiotensin-converting enzyme inhibitors in which emphasis is placed on the action of these

TABLE V Modish Terms for Myocardial Damage

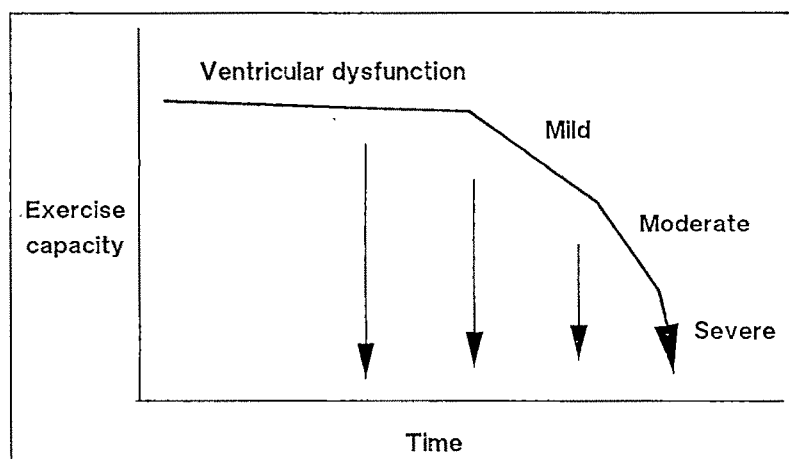
Stunned myocardium ²¹
Hibernating myocardium ²²
Mummified myocardium ²³
Stuttering ischemia ²⁴
Preconditioned myocardium ²⁵
Chronic ischemia
Ischemic cardiomyopathy

drugs on the kidney and subsequently on the arterial resistance in blood vessels subserving exercise in skeletal muscle. This mechanism would suggest a different mode of action for angiotensin-converting enzyme inhibitors compared to vasodilators. An alternative argument is that the benefit is due solely to a decrease in the wall stress of the myocardium. If that were so, then all vasodilators and angiotensin-converting enzyme inhibitors should have an effect dependent upon their action on the central hemodynamics. This is a matter that needs to be resolved.

The key question at the present time is how early vasodilators and angiotensin-converting enzyme inhibitors should be introduced in the treatment of CHF. Most physicians would use these drugs when patients are on, for example, frusemide 80 mg. Since diuretics used in the treatment of CHF activate the renal angiotensin system, there is an argument that angiotensin-converting enzyme inhibitors should be used earlier in the treatment of CHF. Angiotensin-converting enzyme inhibitors alone are not sufficient for the treatment of patients who have had a past episode of sodium retention.²⁵

Antiarrhythmic agents and anticoagulants: Patients with CHF commonly have ventricular arrhythmias and sudden death is said to be common.²⁶ However, most of these studies have defined sudden death as death within 6 hours of being seen alive and well. That is not a helpful definition because 6 hours is ample time for a patient to die either of progressive CHF or from an ischemic episode. It is unknown how many deaths from CHF are attributable to an opportunistic arrhythmia rather than due to progression of CHF. A preliminary

FIGURE 3. Progression of heart failure. Some patients will die prematurely from a cardiac event rather than progressively deteriorate.



report of a recent trial with amiodarone in patients with CHF did not provide any support for the use of antiarrhythmics in such patients. The results of the Cardiac Arrhythmia Suppression Trial study²⁷ also do not provide support for the treatment of ventricular premature beats in asymptomatic patients with atheromatous coronary artery disease. A further controversy regards the use of anticoagulants in patients with dilated cardiomyopathy. These patients are at risk of embolic events, but treatment with anticoagulants also carries an appreciable risk. At present, only selected patients should be treated with anticoagulants.

Drugs for the future: On the basis of recent experience with positive inotropic drugs, which have been under active investigation for the treatment of CHF, the future outlook for such drugs may be limited to intermittent use or limited for use in patients with almost terminal CHF. Likewise, unselective systemic vasodilators, as a group, seem unlikely to have a major impact. The use of β antagonists continues to be investigated in carefully selected patients and there are many reasons why in some circumstances, β blockade may have a limited advantage. The slowing of the heart rate on exercise can improve diastolic filling. A direct harmful effect of catecholamines on the myocardium may be minimized, arrhythmias may be prevented or down-regulation of β receptors may be reversed. On the other hand, β antagonists have the propensity to worsen CHF, particularly in the severely ill.

Drugs that selectively increase renal blood flow at rest or skeletal muscle blood flow on exercise would be expected to be of more benefit. A totally different approach is to manipulate those factors that control hypertrophy of heart muscle, the development of fibrosis or modify the orientation of myocytes in the heart.

Assessment of patients with heart failure: The presence of CHF predicts death from CHF. Any abnormal-

ity that relates to the severity of CHF will have prognostic significance. Recent studies have shown that the ejection fraction, peak oxygen consumption, plasma sodium and plasma noradrenaline concentration are good predictors of a poor prognosis and are useful in a group of patients with severe CHF. The measurement of the ejection fraction is relatively simple and an estimate can be obtained from an echocardiogram. The measurement of peak oxygen consumption is more complex and requires expensive equipment and staff. New forms of exercise test are being developed that may prove useful in the future, not only to categorize patients with CHF, but to assess the effect of treatment and progress of the disease.^{28,29} Current exercise tests have been largely developed from those used in athletes or patients with angina pectoris. They measure the oxygen consumption in a test of increasing severity. More recently, tests have been devised that measure the extent to which a patient can undertake exercise in a given period of time.²⁹ This test may relate more precisely to everyday activities.

Conclusion: The diagnosis, management and treatment of CHF has, for some time, been the ugly sister of cardiology in comparison to prevention, invasive procedures and thrombolytic therapy for acute myocardial infarction. Advances in understanding CHF and the availability of new drugs have brought about great changes in our ideas of how these patients should be investigated and treated. There are many avenues for progress. The key will be the identification of particular subgroups of patients that will benefit from particular treatments.

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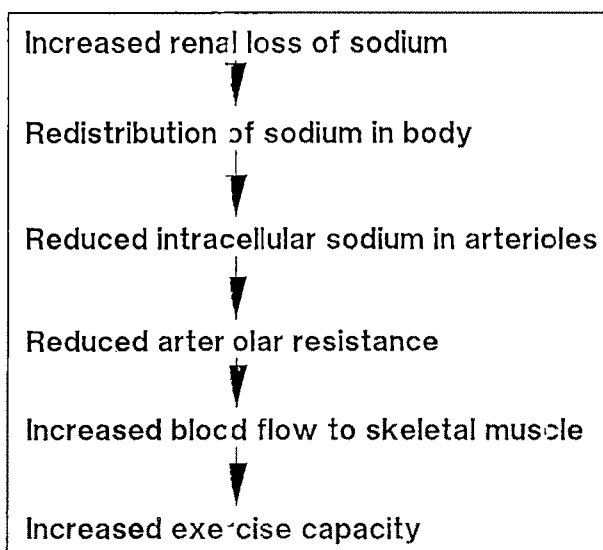


FIGURE 4. A possible mode of action of angiotensin-converting enzyme inhibitors in heart failure. This mechanism would account for differences in efficacy of direct vasodilators and angiotensin-converting enzyme inhibitors.

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Future Perspectives in Basic Science Understanding of Congestive Heart Failure

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Growing appreciation of the poor prognosis in patients with congestive heart failure (CHF), which a few years ago carried a 5-year mortality of approximately 50%,¹ has led to a reevaluation of the goals of therapy for this condition.² Traditionally, treatment of the patient with heart failure has focused on the systemic manifestations of this syndrome, notably salt and water retention, and vasoconstriction. However, these circulatory adjustments to the chronically reduced output by the failing heart, which probably arose during evolution as short-term compensatory mechanisms to aid the body in surviving hemorrhage,³ represent processes that are secondary to abnormal cardiac function.

It is only recently that medical therapy has been re-directed to the cause of this syndrome, the cardiac disorder itself. Whereas our ability to deal with most causes of heart failure is quite limited, growing evidence that medical therapy can improve prognosis in these patients⁴⁻⁶ has highlighted the importance of preventing deterioration of the heart in patients with CHF. Thus, additional understanding of the cellular abnormalities that contribute to progressive failure of the hypertrophied, failing myocardium represents a major goal for future research directed to improving long-term prognosis in these patients.²

Cardiomyopathy of overload: The myocardial abnormalities that are responsible for progressive deterioration of the hearts of patients with CHF remain poorly understood. In some patients, notably those with cardiomyopathies, abnormalities in the cells of the myocardium represent the primary cause of heart failure. However, chronic overloading can itself initiate a sequence of responses that lead to deterioration and death of the cells of the heart.⁷ Thus, in patients with valvular heart disease or in whom portions of the left ventricle have been damaged after myocardial infarction, chronically increased work of the otherwise normal myocardium leads to progressive deterioration of the overloaded myocardial cells. However, the mechanisms by which sustained overloading causes the hypertrophied myocardial cells to deteriorate, die and become replaced by fibrous tissue are not well understood. This process, which represents an unwelcome consequence of the

compensation provided by the increased mass of overloaded myocardium, can be viewed as a "cardiomyopathy of overload" that probably plays an important role in determining the poor prognosis in patients with CHF.⁷

Pathogenesis of the cardiomyopathy of overload:

Although the causes of deterioration of the failing heart remain poorly understood, at least 2 pathogenetic mechanisms appear likely to play a role in this important process. The first is a state of chronic energy-starvation, which probably contributes to impaired function, as well as cell death, in the chronically overloaded heart. Second, complex changes in the composition of the hypertrophied heart may, themselves, be accompanied by abnormalities that cause the chronically overloaded myocardium to deteriorate.

ENERGY-STARVATION IN THE FAILING HEART: At least 3 mechanisms could lead to a state of energy-starvation in the cells of the chronically overloaded heart. Because the adult heart has little or no capacity for cell division, chronic overloading causes each myocardial cell to sustain an increased level of work output. Hypertrophy, by increasing the size of the myocardial cells and thereby augmenting the number of sarcomeres that share the overload, would, of course, reduce the load on each sarcomere. However, the compensation brought about by the increased muscle mass may not perfectly match the increased load; as a result, the rate of energy expenditure by each sarcomere of the hypertrophied heart would remain chronically elevated.

A relative deficiency in the systems that provide high-energy phosphate compounds to meet the increased work of the overloaded heart represents a second cause for chronic energy starvation in the hearts of patients with CHF. In established myocardial hypertrophy, the fraction of cell volume occupied by myofibrils has been found to be increased, relative to mitochondrial mass.⁸⁻¹⁰ The resulting increase in the number of adenosine triphosphate-consuming myofibrils whose increased energy demands must be supplied by a reduced number of adenosine triphosphate-generating mitochondria would, therefore, contribute to a state of chemical energy starvation in the hearts of patients with CHF.

Changes in the architecture of the hypertrophied heart could also exacerbate a state of energy starvation in the hypertrophied, failing heart. These changes include increased intercapillary distance and a decreased number of transverse capillary profiles per mm²,^{8,11} which would increase the diffusion distance for substrates, notably oxygen, essential for energy production by the hypertrophied heart. The lengthened pathway for blood flow from the major epicardial coronary arteries

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through the thickened walls of the hypertrophied ventricle would exacerbate the relative energy deficit in the relatively underperfused subendocardial regions of the ventricle.¹² Studies of the hearts of patients with CHF,^{13,14} which are in accord with earlier studies in animal models,^{15,16} provide direct evidence that high-energy phosphate levels are, in fact, reduced in failing hearts.

Future research is needed to define the extent of a possible energy deficit in CHF. If, in fact, there is serious energy-starvation in some hypertrophied, failing hearts, then clinical approaches must be tailored to specific subsets of patients with CHF and means sought to reduce a high-energy phosphate depletion and reverse detrimental effects of an energy deficit on the heart muscle. As therapeutic strategies for the management of CHF must be evaluated in terms of their impact on long-term prognosis,² data are also needed to define whether the benefits of drugs that unload the failing heart are explained by their energy-sparing effects. This is especially important in light of evidence (see later) that as yet poorly understood actions of several classes of drugs may modify survival in these patients. It is also essential to determine whether the clinical use of inotropic drugs should be limited because of their potential to exacerbate energy starvation in the overloaded, failing myocardium. If, as now appears likely, such a limitation exists, additional studies of the energetics of contraction and relaxation might provide clues as to novel means to

maximize the work output of the failing heart for any given amount of energy expended.

CHANGES IN THE COMPOSITION OF THE HYPERTROPHIED HEART: The myocardial hypertrophy that results from chronically increased cardiac work is accompanied by complex changes in myocardial cell composition.⁷ In the heart's response to chronic overload, altered expression of the genes that encode key myocardial proteins leads to the preferential synthesis of protein isoforms that determine a reduced rate of energy expenditure, and an overall change in composition that leads to the reappearance of proteins that had normally appeared earlier in fetal life.⁷ The extent to which expression of altered gene products in the hypertrophied myocardium contributes to progressive degeneration of the overloaded heart may, in fact, represent the most important question for future research into the causes of the downhill course in these patients. Thus, new understanding of the causes of cell degeneration and death in the cardiomyopathy of overload would be of obvious value in the management of CHF.

Effects of therapy on natural history in patients with congestive heart failure: Recent clinical trials have provided tantalizing clues regarding new avenues for efforts to improve natural history in patients with CHF. Both basic and clinical research are needed to answer at least 2 important questions that have emerged from recent studies of this condition: the effects of positive and negative inotropic interventions on long-term survival,

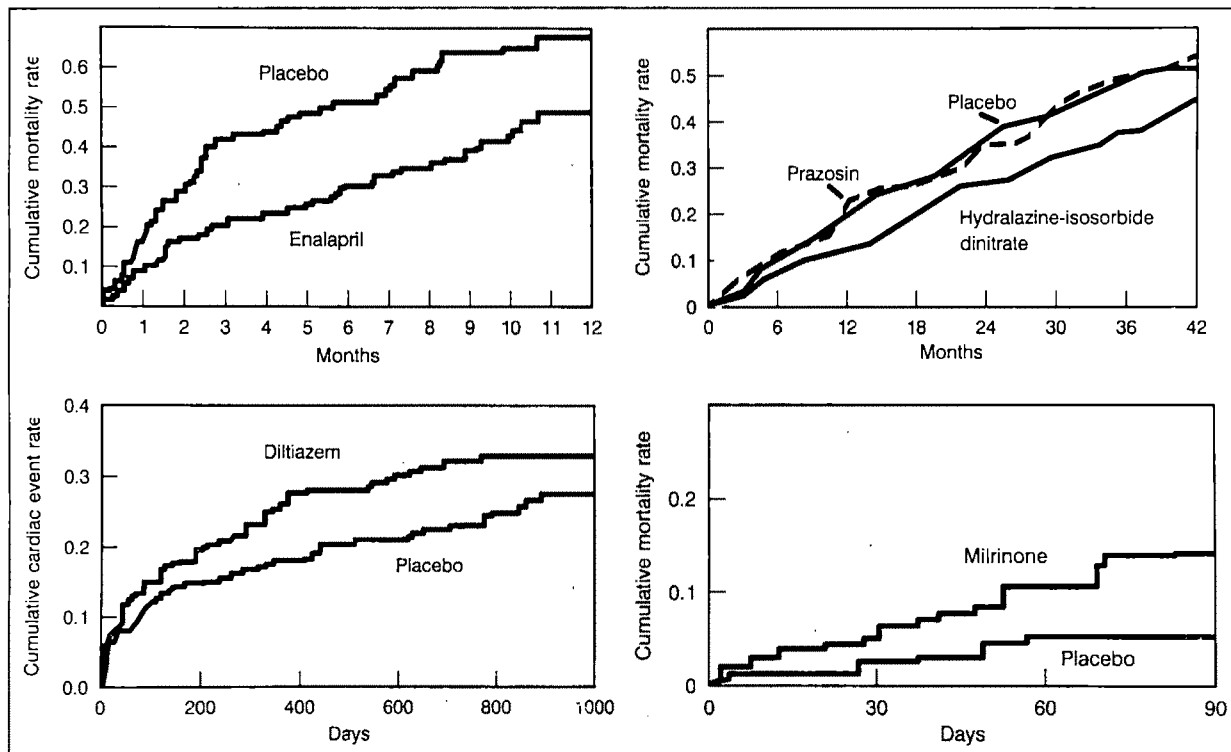


FIGURE 1. Comparison of 4 drugs, each of which has important vasodilator actions, on survival in patients with congestive heart failure. As these data were obtained from 4 independent studies that examined different subsets of patients, care must be exercised in reaching conclusions regarding the existence of true differences between these drugs on survival. However, in the context of this article these data suggest promising directions for future research. The studies from which these data were obtained are: enalapril⁵; hydralazine, isosorbide dinitrate and prazosin⁴; diltiazem²⁷; and milrinone.²⁸

and the mechanisms responsible for apparent differences in long-term survival when patients with CHF are given different vasodilators.

EFFECTS OF POSITIVE AND NEGATIVE INOTROPIC AGENTS: The long-term clinical response to drugs that increase myocardial contractility is of timely interest and importance. Only a few years ago, positive inotropic agents were viewed as specific therapy for patients with heart failure, and there was even a tendency to believe that the more powerful the inotropic action of a drug, the more effective it would be in treating these patients. However, a number of theoretical concerns suggested that positive inotropic drugs might exert significant detrimental long-term effects in patients with CHF; these include worsening of the deficit between energy production and energy utilization, exacerbation of relaxation abnormalities, and arrhythmogenic effects resulting from increased levels of cytosolic calcium and cyclic adenosine monophosphate, intracellular second messengers which activate inward (depolarizing) ion currents that are known to be arrhythmogenic.¹⁷ These considerations probably account for reports that positive inotropic agents can exert detrimental effects in patients with chronic CHF.¹⁸ Conversely, negative inotropic agents have been reported to exert beneficial effects in patients with heart failure.¹⁹⁻²⁴ As the reduction of myocardial contractility that results from altered gene expression in the hypertrophied, failing heart may be compensatory, rather than deleterious, in some patients with heart failure,²⁵ more information is needed to define whether, and in which subsets of patients, this unconventional approach to the therapy of CHF is warranted.

EFFECTS OF DIFFERENT VASODILATORS: There is increasing evidence that drugs which unload the heart not only improve symptoms in patients with CHF, but also increase survival. The likelihood that the failing heart is in an energy-starved state can explain some of the beneficial effects of drugs that, by reducing afterload, decrease energy expenditure by the failing heart. However, additional, but poorly understood, effects of some classes of vasodilators may also slow the progression of the cardiomyopathy of overload in these patients (Figure 1).

Although unloading of the failing heart generally alleviates the symptoms caused by depressed myocardial function in patients with CHF, the effects of different vasodilators on the natural history of this condition are surprisingly variable.²⁵ Whereas any vasodilator would be expected to reduce energy expenditure by an overloaded heart, not all of these drugs improve prognosis. The combination of hydralazine (an arteriolar dilator) and isosorbide dinitrate (mainly a venodilator) has been shown to prolong survival in patients with congestive heart failure⁴; although, in the same study prazosin, an α -adrenergic blocker that exerts both arteriolar and venodilator effects, had no effect on natural history in these patients. In patients with heart failure after myocardial infarction, the calcium channel blocker diltiazem, which is mainly an arteriolar dilator, appeared to worsen prognosis.²⁷ In contrast, the converting enzyme inhibitor enalapril almost doubled life expectancy in a

group of patients with severe left ventricular failure,⁵ a finding that is in accord with other data^{6,26} which suggest that, as a class, the converting enzyme inhibitors slow the progression of the cardiomyopathy of overload in CHF.

The data in Figure 1, which were taken from differently designed studies of a variety of subsets of patients, do not provide conclusive evidence that different vasodilators have variable effects on long-term survival in patients with CHF. However, they do suggest that poorly understood effects of some of these vasodilators may determine their effects on natural history in this chronic condition. New knowledge of the mechanism responsible for the apparent differences in the influences of these drugs on the failing heart may lead to a better understanding of mechanisms that can alleviate the cardiomyopathy of overload in CHF.²⁹ Such knowledge would facilitate the formulation of therapeutic strategies to improve well-being and prognosis in these patients.

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Balloon Angioplasty for Congenital Mitral Stenosis

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We attempted balloon angioplasty in 9 children (ages 0.1 to 10 years) with congenital mitral stenosis. All were symptomatic with severe congestive heart failure and failure to thrive. Effective reduction in mitral gradient was initially achieved in 7 patients. For the entire group, mean valve gradient decreased from 14.8 ± 5.0 to 8.1 ± 6.7 mm ($p = 0.0007$) and mean valve area increased from 1.1 ± 0.5 to 1.8 ± 0.9 cm²/m² ($p = 0.003$). More than mild mitral regurgitation developed in 2 patients but none required surgery for mitral regurgitation. Poor gradient relief followed dilation of valves with unbalanced chordal attachments, with restriction to the valve apparatus as in mitral arcade, and where the obstruction was not purely valvar as it is with a supramitral ring. No strokes, infection or deaths were due to the procedure.

Based on these data, balloon angioplasty of congenital mitral stenosis should be considered before mitral valve replacement in younger patients and in those in whom mitral valve replacement would be problematic.

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The surgical management of congenital mitral stenosis (MS) carries significant morbidity and mortality, particularly in infants and small children. In a recent review of valve replacement in children <5 years of age, there were 6 patients with congenital MS who required mitral valve replacement, of whom 2 died at operation.¹ Even if patients survive surgery, ongoing morbidity occurs due to repeat valve replacement, thrombotic episodes and hemorrhagic complications related to anticoagulation. Therefore, we have investigated the use of balloon angioplasty as an alternative approach to the surgical management of congenital MS in patients without a parachute deformity of the mitral valve. The purposes of this study were to (1) combine our initial experience with balloon angioplasty in congenital MS in 9 patients from 3 centers; (2) describe the follow-up in apparently successful dilations; and (3) report the echocardiographic features of valves that may predict a successful outcome.

METHODS

Patients: Between June 1987 and January 1990, we attempted balloon dilation of the mitral valve in 9 children with congenital MS. The diagnosis of MS was determined from clinical data (Table I) including cardiac ultrasound. All children were symptomatic with congestive heart failure and weighed far below the third percentile for their age. Because of the surgical risks involved, it was decided to attempt balloon angioplasty as the initial procedure. However, those with a parachute deformity of the mitral valve, identified by 2-dimensional echocardiography, were excluded as candidates for balloon valvuloplasty. Before cardiac catheterization, informed consent was obtained from a parent of each patient.

Echocardiographic evaluation: Two-dimensional echocardiography and Doppler examination were performed before dilation (1 to 68 days, median 20) and 1 to 2 days and up to 3½ years after dilation. Color Doppler examination was performed in all patients. Mitral valve morphology and papillary muscle architecture were examined from multiple views. Left atrial volume was estimated assuming a spherical model from the formula $4/3 \pi r^3$, where r was the mean of left atrial dimension measured in transverse, coronal and sagittal planes. Mitral valve annulus diameter at the hinge points of the leaflets was measured from apical and parasternal views and the average calculated.

Doppler recordings of mitral inflow were obtained from an apical 4-chamber view. Maximum instanta-

neous and mean gradients were calculated using the modified Bernoulli equation. The presence and degree of mitral regurgitation were estimated using color and pulsed Doppler from apical and parasternal windows. The degree of regurgitation was estimated by visual inspection of the color Doppler signal on a scale from 0 to 4+: 0, no regurgitation; 1+, trivial, regurgitant jet extending to less than half cavity dimension; 2+, mild, jet extending beyond half cavity diameter; 3+, moderate, jet extending across the entire diameter of the left atrium, but filling <50% of left atrial area; or 4+, severe, jet extending to the top of left atrium and filling >50% of left atrial cross-sectional area.

Cardiac catheterization: Right- and left-sided cardiac catheterization were performed percutaneously from the groin. Local anesthesia and systemic anticoagulation were used.

Initially, left atrial pressure was estimated from the pulmonary capillary wedge pressure but in all patients was measured directly after transseptal puncture. Cardiac output was calculated using the Fick principle. After direct measurement of left heart pressures, a retrograde left ventriculogram was recorded to assess the degree of mitral regurgitation. The amount of regurgitation was graded from 1+ to 4+ using the system previously described by Grossman.²

The technique for percutaneous congenital mitral valve dilation was similar to that previously described by Lock et al³ for rheumatic mitral stenosis. The initial balloon size was selected to be smaller than the annulus diameter as estimated by ultrasound or angiography. The balloon was inflated by hand with dilute contrast material until any constriction of the "waist" disappeared or the balloon was maximally inflated. After each dilation, the gradient was remeasured and a left ventriculography performed to check for the presence of mitral regurgitation. In general, a larger balloon catheter was selected and the dilation procedure repeated until the inflated balloon was up to 30% larger than the

TABLE I Patient Characteristics Before Valvuloplasty

Pt	Age (yr)	Weight (kg)	Mitral Valve Morphology*
1	10.0	18.9	Triple orifice
2	3.8	11.8	Classic congenital MS with annular hypoplasia
3	0.3	4.7	Classic congenital MS†
4	0.4	4.5	Classic congenital MS except for mildly unbalanced chordal attachments†
5	0.1	4.2	Classic congenital MS†
6	0.6	4.8	Classic congenital MS with annular hypoplasia†
7	1.3	8.1	Classic congenital MS but with unbalanced chordal attachments and annular hypoplasia
8	1.2	6.1	Classic congenital MS
9	1.4	6.8	Supramitral ring and annular hypoplasia†
Mean	2.1	7.8	

* Mitral valve morphology refers to morphology as determined by ultrasound before balloon angioplasty.
† Classic congenital MS refers to a valve with 2 left ventricular papillary muscles in which there is reduction of interpapillary distance, obliteration of interchordal spaces and short chordae tendineae.

annulus diameter from angiography, or the mean gradient across the valve decreased $\geq 50\%$, or the degree of mitral regurgitation increased by 1 grade.

Paired *t* tests were used to compare the significance of changes in mean transmitral gradient, mitral valve area, cardiac output, pulmonary artery mean pressure, left ventricular end-diastolic pressure, degree of mitral regurgitation and proportional net intracardiac shunt (Qp/Qs).

RESULTS

Early results of dilation: All patients who underwent catheterization for balloon dilation of congenital mitral stenosis had successful placement of the angioplasty balloon across the valve. The hemodynamic and echo-

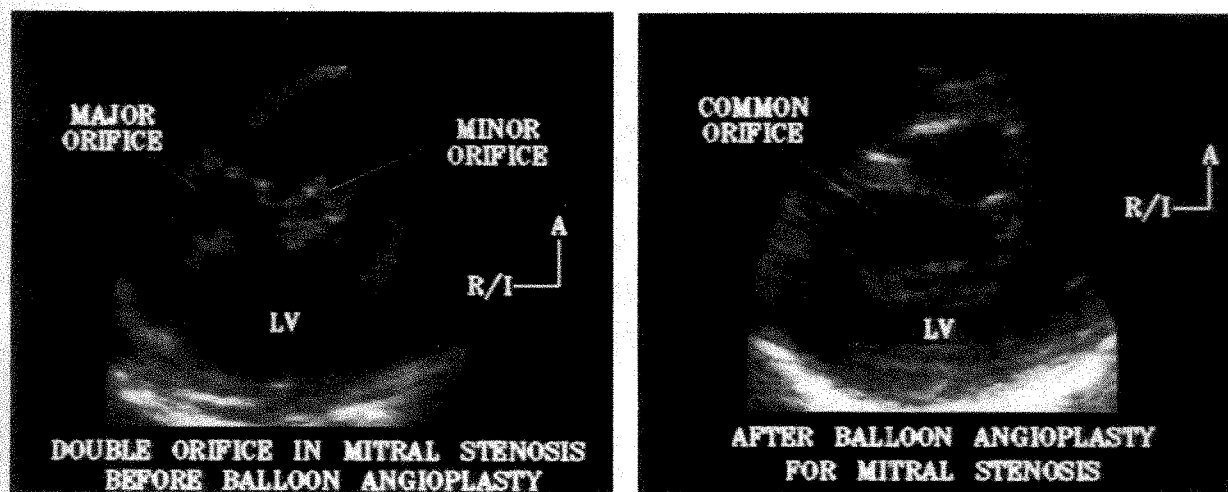


FIGURE 1. Patient 1. Parasternal short-axis views of left ventricle (LV) and mitral valve. Before dilation (*left*), a bridge of tissue separates a major, medial orifice from a minor, more lateral orifice. A third orifice (not shown) is located more apically. After dilation (*right*), the bridging tissue is torn, resulting in a large common orifice. The movement of the anterior (A) and posterior leaflets is nearly unrestricted. R/I = right/inferior.

cardiographic data are summarized in Table II. Some reduction in mitral gradient was initially achieved in 8 of 9 patients (in 1 the gradient decreased because of diminished cardiac output and not because of increased mitral valve area). For the entire group, the mean valve gradient decreased from 14.8 ± 5.0 to 8.1 ± 6.7 mm Hg ($p = 0.0007$) and mean valve area increased from 1.1 ± 0.5 to 1.8 ± 0.9 cm²/m² ($p = 0.003$).

Late results of dilation: Late echocardiographic follow-up data showed persistent gradient relief in 3 patients (nos. 1, 2 and 3). Patient 1, who had a triple orifice mitral valve, had the best result, with nearly a doubling in mitral valve area despite the fact that the balloon-to-anulus ratio was the smallest of any patient. In Figure 1 (left), 2 of the orifices are displayed (the other orifice was more apically located). During dila-

tion, the catheter crossed the more medial orifice. After dilation (Figure 1, right), there was a larger common orifice; the tissue that previously had divided the 2 smaller orifices was presumably torn. With color mapping, flow could be seen moving through the common orifice. Gradient relief persisted ≥ 7 months after balloon angioplasty (mean Doppler gradient only 2 mm Hg) and allowed the child to remain asymptomatic. Mitral regurgitation was not present at last follow-up. Clinically, the child had considerable subjective improvement in her exercise tolerance. Her weight increased from 18.9 kg (far $<3\%$) to 23.4 kg ($>3\%$) in the 7 months after catheterization.

Patient 2, with valve morphology typical of congenital MS, had no Doppler evidence of mitral regurgitation before the procedure and by color Doppler had mild to

TABLE II Hemodynamics Before and After Angioplasty and Balloon—Anulus Characteristics

Pt	Valve Area Index (cm ² /m ²)			Mean Valve Gradient (mm)		
	Before	After	% Change	Before	After	% Change
1	1.3	2.3	77	16	6	61
2	1.1	1.6	42	16	10	40
3	1.1	1.9	79	13	3	77
4	0.7	1.0	51	16	6	59
5	1.7	2.6	53	6	4	33
6	0.8	1.6	103	15	5	64
7	1.8	3.1	72	~15 [†]	8	50
8	—	—	—	25	25	0
9	0.5	0.4	-15	11	6	43
Mean ± SD	1.1 ± 0.5	1.8 ± 0.9	58 ± 33*	14.8 ± 5.0	8.1 ± 6.7	48 ± 21*
	PA Mean Pressure (mm)		LV End-Diastolic Pressure (mm)		Mitral Regurgitation (grade)	
	Before	After	Before	After	Before	After
1	27	23	2	4	1	1
2	40	—	12	8	0	1
3	37	43	18	11	0	1
4	40	60	12	17	0	1
5	24	—	13	14	1	1
6	44	28	18	13	0	2
7	53	73	10	16	1	1
8	57	—	18	14	1	1
9	44	40	20	20	1	2
Mean ± SD	41.8 ± 12.5	44.5 ± 19.0	13.2 ± 5.2	13.0 ± 4.6		
	Cardiac Index (liters/min/m ²)		Anulus Diameter (mm)	Balloon-Anulus Ratio (%)		
	Before	After				
1	4.3	5.9	34	54		
2	3.7	3.4	15	100		
3	3.5	2.7	12	85		
4	2.8	3.1	14	59		
5	3.5	3.9	12	69		
6	3.1	2.6	12	87		
7	5.6	6.7	13	115		
8	—	—	17	70		
9	2.4	1.4	11	112		
Mean ± SD	3.6 ± 1.0	3.7 ± 1.8	15 ± 7	83 ± 22		

* Using paired t test, change from before versus after dilation significant at p <0.005.
[†] Gradient based on mean capillary wedge pressure. All other mean gradients reported are based on directly measured left atrial pressure.
Anulus diameter based on echocardiographic measurement.
LV = left ventricular; PA = pulmonary artery.

moderate regurgitation after dilation. The increased regurgitation was related to prolapse of the anterior leaflet of the mitral valve (Figure 2). The stenosis was partially relieved, with the mean gradient by Doppler decreasing from 15 to 10 mm Hg. Although this patient had less severe congestive failure and continued reduction in the mitral valve gradient, the procedure has not yet resulted in accelerated somatic growth.

Patient 3 symptomatically improved after the procedure and catch-up growth occurred. Follow-up ultrasound study showed some increase in mean Doppler gradient but not to levels before dilation.

The 2 most recent patients (nos. 4 and 5) had an initial reduction in gradient and >50% increase in valve area. In both babies the weight was >5 kg at the time of dilation. In patient 4, the gradient decreased nearly 60% and valve area increased by 50%, allowing weaning from mechanical ventilation.

Late restenosis after dilation: Surprisingly, 2 patients who had an initial reduction in gradient developed worsening failure within 2 months after balloon angioplasty. Patient 6 had MS, coarctation, subaortic stenosis and multiple ventricular septal defects. Before mitral valve dilation was performed, the child had required coarctation repair, pulmonary artery band and resection of a supramitral ring. With angioplasty, the mean gradient decreased from 15 to 5 mm Hg, but increased to 13 mm Hg at later catheterization, without changes in cardiac output. This patient had moderate mitral regurgitation immediately after dilation. The mitral anulus was hypoplastic with a diameter of 12 mm, considered too small to allow valve replacement at the anular level. In addition, the normal left atrial size complicated supraannular mitral valve replacement. After angioplasty, the anterior leaflet had a small tear; after initial relief, the gradient redeveloped and the regurgitation increased. The left atrial volume increased from 116 cm³/m³ before dilation to 172 cm³/m³ 22 days later. Anulus diameter did not change over the same interval. The patient then underwent successful mitral valve replacement. A 17-mm Bjork-Shiley valve was placed in the supraannular position because the anulus was still too small.

Patient 7 also had MS with aortic coarctation and ventricular septal defect. After coarctation repair, the child continued to have severe congestive failure and had suprasystemic pulmonary artery pressure. Two left ventricular papillary muscles were noted on ultrasound, but the chordal attachments were weighted to the larger posteromedial group. With balloon angioplasty, the gradient decreased from 15 to 8 mm Hg. After a few weeks the patient developed worsening failure and recatheterization confirmed the clinical impression of recurrence of MS because the gradient had increased to 12 mm. The patient was referred for surgery. The surgeon noted a lack of the usual interchordal spaces as well as the usual commissures and he performed a mitral commissurotomy. This child died from infection and multisystem failure 4 months after a complicated and poorly tolerated course. At autopsy, the valve had a major posteromedial and a hypoplastic anterolateral papillary

muscle. Predominant attachments of the chordae tendineae were to the posteromedial papillary muscle group.

Failed dilations: Two patients did not achieve a satisfactory initial result (nos. 8 and 9). Patient 8 had little change in the appearance of the valve echocardiographically. The papillary muscles were close together and, while it was not appreciated antemortem, at postmortem examination a fibrous ridge typical of mitral arcade was noted. Attempts to use a larger balloon size were unsuccessful because the balloon straddled the atrial septum during dilation and limited full inflation. This patient was clinically unchanged after dilation, and was referred for surgery and died in the operating room after mitral valve replacement.

Patient 9 had previously undergone resection of a supramitral ring and a mitral commissurotomy. Residual supra- and valvar obstruction occurred. Balloon dilation was attempted but did not increase the valve area and the child required surgery soon thereafter. A supra-valvular ring was resected. A prosthetic valve had to be placed in the supraannular position because of the hypoplastic mitral anulus.

For the entire group of patients, there was no significant change immediately after dilation in left ventricular end-diastolic pressure, pulmonary artery mean pressure or cardiac index.

Complications: Two patients (nos. 6 and 9) with the smallest anuli in the group developed more than mild mitral regurgitation immediately after dilation.

None of the patients had significant atrial septal defects before dilation (1 infant had a tiny sprung foramen ovale). Consequently, all required a transseptal (Brockenbrough) approach. A small atrial level left-to-right shunt was detected by color Doppler after balloon angioplasty in 7 of 9 patients with the largest Q_pQ_s being 1.2 to 1.

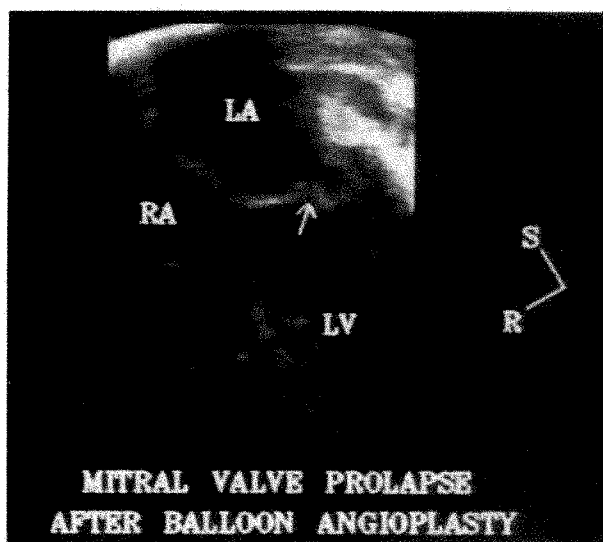


FIGURE 2. Patient 2. Apical image of the mitral valve after dilation. There is prolapse of the anterior leaflet (tip of arrow) that results in incomplete coaptation of the valve leaflets and mitral regurgitation. LA = left atrium; LV = left ventricle; R = right; RA = right atrium; S = superior.

Blood loss was estimated to exceed 10 ml/kg in 4 patients. Fluoroscopy time ranged from 61 to 135 minutes. One patient required intubation during catheterization because of respiratory acidosis. No strokes, infections or deaths were due to the procedure; both deaths in this series followed valve surgery.

DISCUSSION

The management of the infant or small child with symptomatic MS is a very difficult problem. Current surgical therapy carries significant mortality and morbidity. When valve replacement is performed, surgery is in many cases palliative, since in rapidly growing children the valve will often need to be changed within 3 to 4 years.¹

There are 2 previous case reports of balloon angioplasty for congenital MS. In the report of 2 cases by Kveselis et al⁴ the procedure was completed in 1, with stenosis being only minimally relieved with the valve area increasing 21%. Late follow-up was not available. A single case of balloon angioplasty in congenital MS in a 3-year-old child was reported by Alday and Juaneda,⁵ the procedure resulting in an increase of the mitral valve area, although follow-up was only 1 month.

We have dilated mitral valves in 9 children with congenital MS. Although patients with true parachute mitral valves were excluded, we did dilate all nonparachute mitral valves regardless of anatomy. The procedure itself was performed with minimal morbidity and no mortality. Initial gradient relief was achieved in 7 of 9 cases. The reduction in the degree of MS was clinically effective in 5 cases, and in 3 the gradient relief has persisted >3 months, the most successful result being in a patient with a triple orifice valve. The morphology of multiple orifice mitral valve is variable, and in only a portion is there a thin central fibrous subdivision between the multiple orifices as in the patient in this series.⁶ Tearing of fibrous bridges could potentially result in instability of the valve leaflets and the development of mitral regurgitation.

In 1 patient, while dilation did not result in long-term relief of MS, angioplasty produced mitral regurgitation that contributed to increased left atrial size and

facilitated supraannular placement of a mitral prosthesis. Relatively poor results were achieved in children who had "parachute-like" valves with disproportionate chordal attachments to 1 of their papillary muscles, in those with restriction of the valve apparatus as in mitral arcade, and in those with a small anulus. A satisfactory result was not achieved when obstruction was due to a supramitral ring.

The results of this study must be interpreted with caution. The varying anatomic valve types, the differences in balloon sizes and limitations in precisely defining anatomy may have contributed to these variable results.

The aforementioned data would support several inferences: a successful outcome from balloon dilation is unlikely in all patients with congenital MS; balloon angioplasty may be more likely to achieve favorable results in patients with balanced chordal attachments and in some patients with stenotic multiple orifice valves; and, in some cases, early gradient relief may be followed by restenosis. Nonetheless, balloon angioplasty of congenital MS should be considered before mitral valve replacement in younger patients (<5 years old) and in those with a hypoplastic mitral anulus for whom mitral valve replacement would be problematic.

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Effect of Plasma Volume Expansion on Hemodynamics and Atrial Natriuretic Factor Release in Heart-Transplant Recipients

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Plasma atrial natriuretic factor (ANF), plasma cyclic guanosine monophosphate (cGMP), plasma aldosterone, plasma-renin activity (PRA) and hemodynamic parameters were measured in heart-transplant recipients and control patients (chest pain syndrome) during right-sided heart catheterization under basal conditions and in response to an intravenous saline load. Basal plasma ANF and cGMP were higher in heart-transplant recipients than in control patients, whereas PRA and plasma aldosterone did not differ. The high plasma ANF levels in heart-transplant recipients did not result from high atrial pressures but appeared to be related with elevated atrial dimensions and cyclosporine-induced renal failure. During volume expansion, plasma ANF increased in control patients and remained elevated during the postinfusion period. In heart-transplant recipients, the changes in plasma ANF were less marked despite identical increases of atrial pressures. The sluggish response of plasma ANF in this group was associated in the postinfusion period with a nonreturn of the hemodynamic parameters to their basal values in contrast with what was observed in control patients.

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It is now widely admitted that the release of atrial natriuretic factor (ANF) by atrial stretch represents a physiologic mechanism involved in maintenance of homeostasis in response to volume expansion.^{1,2} Cardiac innervation is not necessary for ANF release, which has been found to occur in vitro from atrial fragments³ and in vivo in dogs with surgically denervated hearts.⁴ On the contrary, because increased plasma ANF levels have been reported in heart-transplant recipients,^{5,6} the question may be asked whether cardiac denervation increases ANF secretion. However, factors other than interruption of cardiac nervous pathways may be implicated in increased plasma levels of ANF of heart-transplant recipients, such as the increased atrial dimensions and myocardial mass due to persistence of a cardiac remnant containing a rim of the native atria,⁷ the renal insufficiency related to cyclosporine treatment⁸ and possible changes in atrial functions.⁹ In order to investigate the determinants of ANF secretion from a denervated human cardiac allograft, we have compared the effects of volume expansion on plasma ANF and cardiac hemodynamic parameters during right-sided heart catheterization in heart-transplant recipients and patients investigated for chest pain syndrome who were taken as control patients.

METHODS

Patient selection: Thirteen heart-transplant recipients (mean age 49 ± 9 years) were investigated for routine invasive cardiac evaluation within the first year after orthotopic heart transplantation. All patients received immunosuppressive therapy with prednisolone (0.2 to 0.3 mg/kg/day) and cyclosporine adjusted to maintain blood concentration between 250 to 400 ng/ml (monoclonal antibody technique) or 700 to 1,000 ng/ml (polyclonal antibody technique). Azathioprine (1.0 to 1.5 mg/kg/day) was administered to 7 patients. Sex, age, interval from operation to study, underlying pathology of the heart and treatment of each patient are listed in Table 1. All patients had sinus rhythm and none had a history of atrial fibrillation. Antihypertensive treatments (calcium antagonists and/or diuretics) were interrupted 2 days before the study.

Eight control patients (mean age 54 ± 2.5 years) were studied for possible coronary disease. They did not show historical or electrocardiographic signs of myocardial infarction. All had normal findings on bidimensional and Doppler echocardiographic examinations (no

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TABLE I Clinical Characteristics of Heart-Transplant Recipients

Patients	Age (yrs)	Sex (M/F)	Interval from Surgery to Study (Months)	Underlying Pathology of the Heart	Drugs
1	61	M	3	CAD	C,P,A,Fu,N
2	44	M	2	CAD	C,P,A,N
3	55	M	6	CAD	C,P,A,N
4	50	M	6	CAD	C,P,N
5	59	M	6	CAD	C,P
6	56	M	3	CAD	C,P
7	45	M	9	CAD	C,P,Fu
8	55	M	2	CAD	C,P,A
9	49	M	5	CAD	C,P,A,N
10	39	M	1	DC	C,P,A
11	49	F	4	DC	C,P
12	55	M	10	DC	C,P,A,Fu
13	25	M	4	DC	C,P,N
Mean \pm SEM	49.4 \pm 2.7	12/13	4.7 \pm 0.7		

A = azathioprine; C = cyclosporine; CAD = coronary artery disease; Fu = furosemide; DC = dilated cardiomyopathy; N = nicardipine; P = prednisone.

TABLE II Results of Left Ventricular Angiography and of Coronary Arteriography in Control Patients

Patient	Age (yr)	Sex	LVEDV (ml/m ²)	EF (%)	Coronary Arteriography (% diameter narrowing)		
					LAD	LC	Right
1	40	M	84	65	80	0	0
2	49	F	69	74	0	0	0
3	50	M	85	61	0	0	80
4	52	M	69	67	80	80	0
5	58	M	98	66	0	0	0
6	60	F	68	65	0	0	0
7	60	M	60	72	30	0	30
8	60	M	67	81	0	0	0
Mean \pm SEM	54 \pm 2		75 \pm 4	69 \pm 2			

EF = ejection fraction; LAD = left anterior descending; LC = left circumflex artery; LVEDV = left ventricular end-diastolic volume.

valvular heart disease and no left ventricular hypertrophy). None was hypertensive. Sex, age, individual results of left ventricular angiography and coronary arteriography of each patient are listed in Table II. Among those patients, 4 had normal coronary arteriograms. As in the group of heart-transplant recipients, all patients had sinus rhythm and no history of atrial fibrillation. All treatments (antihypertensive drugs and/or coronary vasodilating drugs) were interrupted 2 days before the study.

All patients had given their informed consent to the protocol that had been previously accepted by the local ethics committee of the Henri Mondor hospital.

Catheterization procedure: Right-sided heart catheterization was performed after the patients gave informed consent. All patients were in the fasting state for ≥ 12 hours before the procedure. No premedication was administered and local anesthesia was obtained with 1 % lidocaine.

A 7Fr Swan-Ganz thermodilution catheter (Edwards Laboratories) was placed into the pulmonary artery through a femoral vein for cardiac output determination (Cardiac Output Computer Model COM-1RS, Edwards Laboratories) and pulmonary artery and pulmonary wedge pressure measurements. A 6Fr angiographic catheter (Cordis Europa N.V. Roden) was

placed into the right atrium through the same femoral vein for right atrial pressure recording and saline infusion. A 3Fr short catheter was placed into a femoral artery for mean arterial pressure recording in heart transplant recipients. In control patients, aortic pressure was recorded through a 6Fr pig-tail angiographic catheter (Cordis Europa N.V.) placed into the aorta via the right femoral artery.

Protocol: After an interval of 15 minutes, basal pressures were recorded, cardiac output was measured and blood samples were obtained (t0). The entire procedure was repeated, for the first time after a 500 ml 0.9% saline infusion into the right atrium at a rate of 100 ml/min (t1), for the second time after another 500 ml infusion of 0.9% saline at the same rate (t2) and for the third time 20 minutes after the end of saline infusion (t3). Then, 30 ml ioxaglate meglumine were injected into the right atrium in order to get angiograms of the 4 chambers. This cardiac angiography was achieved in the 2 groups of patients by electrocardiography-gated digital subtraction technique (General Electric CGR DG 300) at a rate of 25 frames/s on a 256 pixel matrix in an anteroposterior projection. In the control group, left ventricular angiography and coronary arteriography were realized at the end of the study. In the transplanted group, a right ventricular endomyocardial biopsy

performed at the end of the study showed no histologic signs of rejection in all patients.

Data analysis and calculation: Cardiac output and cardiac index were determined by the thermodilution method. Heart rate, arterial pressure, right atrial pressure, pulmonary artery and pulmonary wedge pressures, systemic vascular resistances and pulmonary vascular resistances were calculated by a catheterization data analysis computer system (Model 5600M, Hewlett-Packard) that performed on-line analysis of 9 beats for averaging respiratory variations.

Maximal area projections (absolute and indexed to body surface area) of left and right atria were determined on angiograms by planimetry. Actual areas (cm^2) were calculated after correction for x-ray magnification by recording a frame of a calibrated grid located at the midthoracic level. An estimate of atrial wall stress was obtained by multiplying maximal atrial area by maximal pressure recorded 20 minutes after the end of saline infusion (right atrial pressure for the right atrium and pulmonary wedge pressure for the left atrium).

Laboratory determinations: Blood was collected from the right atrium into vacutainer tubes containing dipotassium ethylenediamine tetraacetate and centrifuged immediately at 4,000 rpm for 20 minutes at 4°C . Plasma ANF was extracted from a 2 ml plasma aliquot on a C-18 octadecylsilane cartridge (Sep-Pak, Waters Associates) and measured by a specific radioimmunoassay as reported elsewhere.¹⁰ Cyclic guanosine monophosphate (cGMP) was also measured after extraction by ethanol using a commercial kit (The Radiochemical Centre). Plasma aldosterone and plasma-renin activity (PRA) were measured in all plasma samples according to Pham Huu Trung and Corvol¹¹ and Menard and Catt,¹² respectively. Plasma epinephrine and norepinephrine were assayed only in the initial (t_0) venous

TABLE III Baseline Data in Control Patients and Heart-Transplant Recipients

Parameter Studied	Control Patients (n = 8)	Heart-Transplant Recipients (n = 13)	p Value
Heart rate (beats/min)	71 \pm 3	93 \pm 4	<0.01
Mean arterial pressure (mm Hg)	97 \pm 4	96 \pm 6	NS
Mean right atrial pressure (mm Hg)	4 \pm 1	5 \pm 1	NS
Mean pulmonary artery wedge pressure (mm Hg)	7 \pm 1	9 \pm 2	NS
Cardiac index (liters/min/ m^2)	3 \pm 0.1	3 \pm 0.2	NS
Systemic vascular resistance (mm Hg/liters/min)	16 \pm 1	20 \pm 2	NS
Mean pulmonary artery pressure (mm Hg)	13 \pm 1	18 \pm 3	NS
Pulmonary vascular resistance (mm Hg)	1 \pm 0.1	2 \pm 0.4	NS
Arterial venous oxygen difference (ml/100 ml)	4 \pm 0.2	5 \pm 0.3	NS
Plasma creatinine ($\mu\text{mol/L}$)	81 \pm 6	139 \pm 12	<0.01
Plasma epinephrine (ng/liter)	84 \pm 26	69 \pm 19	NS
Plasma norepinephrine (ng/liter)	153 \pm 37	321 \pm 34	<0.01
Plasma osmolality (mOsm/kg)	288 \pm 1	293 \pm 1	<0.05

Data are mean \pm standard error of the mean.
NS = nonsignificant.

blood collection according to Mefford et al.¹³ Plasma creatinine was measured using the usual technique adapted to a Technicon autoanalyzer and plasma osmolality was determined by cryoscopy.

Statistical analysis: Data are given as mean \pm standard error of the mean. Comparisons within the same group were performed using 2-factor (patients, time of blood collection) analysis of variance or Student's *t* test for paired values. The relations between plasma ANF concentration and other parameters were analyzed by

FIGURE 1. Time courses of mean right atrial pressure (RAP), mean pulmonary artery pressure (PAP), mean pulmonary wedge pressure (PWP), mean arterial pressure (AP), heart rate (HR), cardiac index (CI), pulmonary vascular resistance (PVR), systemic vascular resistance (SVR) and arterial-venous oxygen difference (VO_2) before (t_0), during (t_0 - t_1 and t_1 - t_2) and after (t_3) an intravenous sodium load in 2 groups of heart-transplant recipients (open squares) and control patients investigated for a chest pain syndrome (closed squares). Changes with time were significant for RAP, PAP, PWP, CI, SVR and VO_2 in both groups ($p < 0.01$) and for AP in the transplanted group ($p < 0.05$). Differences between groups were significant for HR ($p < 0.01$) and PAP at t_3 ($p < 0.05$).

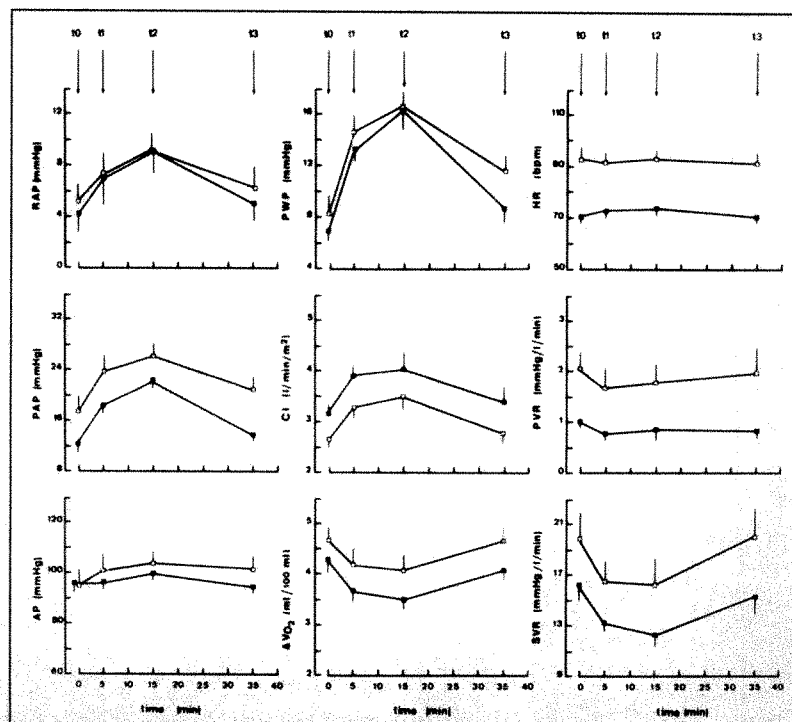


TABLE IV Atrial Dimensions and Estimate of Atrial Wall Stresses in Control Patients and Heart-Transplant Recipients

Patients	S _{RA} (cm ²)	S _{RAi} (cm ² /m ²)	Pmax _{RA} (mm Hg)	S _{RA} X Pmax _{RA} (mm Hg cm ² /m ²)	S _{LA} (cm ²)	S _{LAi} (cm ² /m ²)	Pmax _{LA} (mm Hg)	S _{LA} X Pmax _{LA} (mm Hg cm ² /m ²)
Control								
1	25	14	7	97	22	13	9	113
2	34	21	12	250	34	21	16	330
3	30	16	13	213	49	27	16	427
4	23	15	2	29	35	23	8	182
5	17	10	5	51	22	14	9	122
6	26	13	8	105	32	16	10	163
7	22	10	9	90	31	14	13	185
8	19	10	5	50	37	19	12	232
Mean ± SEM	25 ± 2	14 ± 1	8 ± 1	111 ± 28	33 ± 3	18 ± 2	12 ± 1	219 ± 38
Transplanted								
1	30	17	9	154	53	30	14	419
2	52	29	28	823	57	32	25	810
3	26	14	10	138	38	20	14	286
4	34	19	11	210	48	27	20	538
5	33	18	5	92	55	30	11	334
6	28	15	7	103	58	30	11	332
7	40	21	6	127	51	27	14	375
8	28	18	3	53	29	18	6	109
9	45	28	8	223	52	32	14	445
10	52	33	5	167	49	32	9	285
11	29	15	9	136	36	19	21	403
12	26	14	15	206	50	27	22	583
13	33	17	6	100	52	26	11	287
Mean ± SEM	35 ± 3	20 ± 2	9 ± 2	195 ± 54	48 ± 2	27 ± 1	15 ± 2	400 ± 48
p Value	<0.01	<0.05	NS	NS	<0.001	<0.001	NS	<0.02

NS = not significant; SEM = standard error of the mean; S_{LA} = left anterior surface; S_{LAi} = indexed left atrial surface; S_{LA} X Pmax_{LA} = estimate of left atrial wall stress; S_{RA} = right atrial surface; S_{RAi} = indexed right atrial surface; S_{RA} X Pmax_{RA} = estimate of right atrial wall stress; Pmax_{LA} = left atrial maximum pressure; Pmax_{RA} = right atrial maximum pressure.

linear regression procedure. Comparisons between the 2 groups were performed using Student's *t* test for unpaired values or covariance analysis.

RESULTS

Hemodynamic data: Under basal conditions, heart rate was higher in heart-transplant recipients than in control patients (*p* < 0.01). All the other hemodynamic parameters were not significantly different in the 2 groups (Table III).

In the control patients, saline infusion resulted in an increase of right atrial, pulmonary artery and pulmonary wedge pressures and of cardiac index (*p* < 0.01). Systemic vascular resistances and arterial-venous oxygen difference were significantly decreased (*p* < 0.01). Heart rate, mean arterial pressure and pulmonary vascular resistances did not vary significantly. All values, except pulmonary artery pressure, had returned to their basal levels 20 minutes after the end of the intravenous saline load (t3, Figure 1). Comparison between the 4 patients with normal coronary arteriography and the 4 patients with coronary artery disease revealed similar data for all the parameters during the whole procedure.

In heart-transplant recipients, right atrial, pulmonary artery and pulmonary wedge pressures and cardiac index increased significantly (*p* < 0.01) during the infusion of saline (t0-t1 and t1-t2). Systemic vascular resistances and arterial-venous oxygen difference were decreased (*p* < 0.01). Mean arterial pressure increased (*p* < 0.05) at the end of the infusion of saline (t2). Heart rate and pulmonary vascular resistances were not altered during the procedure. However, 20 minutes after the end of the infusion (t3), pulmonary artery pressure

and pulmonary wedge pressure as well as mean arterial pressure had not returned to basal values (*p* < 0.01 for the first 2; *p* < 0.05 for the latter), as had right atrial pressure, cardiac index, arterial-venous oxygen difference and systemic vascular resistances (Figure 1).

Comparison between the 2 groups showed differences only for heart rate, which remained higher in the transplanted group during the whole procedure (*p* < 0.01), and for pulmonary artery pressure, which was higher in the transplanted group 20 minutes after the end of the saline load (t3; *p* < 0.05).

Atrial dimensions and estimate of atrial wall stresses: These parameters were measured only once at the end of the study. Absolute and indexed area projections of both the right and left atrium were significantly higher in heart-transplant recipients than in control patients. In contrast, right atrial and pulmonary wedge pressures measured simultaneously were similar in both groups. Although there was a trend of the estimate of the wall stress of the right atrium to be higher in transplanted patients, this parameter was significantly higher than in control patients only for the left atrium (Table IV).

Hormonal parameters: Under basal conditions (t0), plasma ANF and plasma cGMP were higher in heart-transplant recipients than in control patients by 2.6 and 2.3 times, respectively (*p* < 0.01). In contrast, PRA and plasma aldosterone were not significantly different. Plasma norepinephrine was also higher in heart-transplant recipients (*p* < 0.01), whereas plasma epinephrine was not significantly different in both groups.

In the control patients, plasma ANF progressively increased during the saline infusion (+41% at t2; *p* < 0.05). It remained elevated at 20 minutes after the

end of the infusion (t3). Plasma cGMP and PRA did not change significantly in response to the saline infusion, even if there was a trend toward PRA decrease, which was the most marked initially (t1; $p = 0.07$). Plasma aldosterone decreased significantly during and after the infusion ($p < 0.01$), the concentration reached at t3 being $< 50\%$ of the basal value (Figure 2).

In the heart-transplant recipients, there was a trend of plasma ANF to increase with saline infusion ($+19\%$ at t2), but the level of significance was not reached. Plasma cGMP and PRA did not change significantly in response to saline infusion. Only plasma aldosterone decreased over the whole period studied. It reached 56% of its basal value 20 minutes after the end of the sodium load (t3, Figure 2).

At any time, plasma ANF and cGMP were higher in the heart-transplant recipients than in the control patients ($p < 0.01$). In contrast, there were no significant differences between both groups for PRA and plasma aldosterone, although PRA tended to be higher in heart-transplant recipients. No significant difference was observed between the absolute increases of plasma ANF at the end of the infusion period (t2-t0) in both groups.

Relations between hormonal and hemodynamic parameters: Comparison between Figures 1 and 2 shows that plasma ANF and cGMP remained elevated after the end of saline infusion (t3) whereas right atrial and pulmonary wedge pressures decreased rapidly. Parallelism between plasma concentrations of these 2 parameters and atrial pressures was observed only during the saline infusion. Therefore, for the correlation calculations we used only the results obtained initially (t0) and during the infusion (t0-t1, t1-t2). We were unable to find any significant relation between plasma ANF and right atrial pressure or pulmonary wedge pressure, the latter being considered as reflecting the left atrial pressure, in heart-transplant recipients as well as in control patients. Covariance analysis showed that plasma ANF was higher ($p < 0.01$) in heart-transplant recipients than in control patients for a given right atrial pressure or a given pulmonary wedge pressure.

We also correlated plasma ANF measured at the end of the saline infusion with the parameters calculated from the data of the cardiac angiography. We first pooled the results of both groups. Plasma ANF was significantly correlated with left atrial indexed surface ($p < 0.01$) and the estimate of left atrial indexed wall stress ($p < 0.05$). A borderline significance ($p = 0.051$) was obtained for the correlation between plasma ANF and left atrial pressure. Plasma ANF was also significantly correlated with right atrial indexed surface ($p < 0.05$) but not with right atrial pressure and the estimate of right atrial indexed wall stress. No significant correlation was found when both groups were studied separately.

Other relations: Plasma ANF was significantly correlated with plasma cGMP in both groups ($p < 0.05$ for the control group and $p < 0.001$ for the transplanted group) when the results obtained at all times of the study were pooled. The slope of the regression line was significantly higher ($p < 0.05$) in the transplanted group

(0.026 pmol/pg) than in the control group (0.017 pmol/pg) indicating that, for a given value of plasma ANF, plasma cGMP was greater in the heart-transplant recipients.

Plasma ANF measured under basal conditions (t0) was significantly correlated ($p < 0.01$) with plasma creatinine when the data of both groups were pooled. A similar significant relation was observed between both parameters measured at the end of the study (t3).

DISCUSSION

The results presented in this report clearly show that plasma ANF and its second messenger, cGMP, are elevated in heart-transplant recipients under basal conditions and after an intravenous saline load. High plasma ANF levels have been previously reported in such patients.^{5,6} In contrast with the findings of Myers et al.,⁶ who noted a discrepancy between an exaggerated response of plasma ANF and a normal response of urinary cGMP to immersion in cardiac transplant recipients, we observed in parallel elevated ANF and cGMP plasma levels. Both parameters were significantly correlated in both groups. The significant relation between ANF and plasma cGMP in heart-transplant recipients suggests that the elevation of plasma ANF in these patients corresponds to biologically active forms.

The reasons why plasma ANF is high in heart-transplant recipients are probably multiple. Mean right atrial pressure and mean pulmonary wedge pressure, which

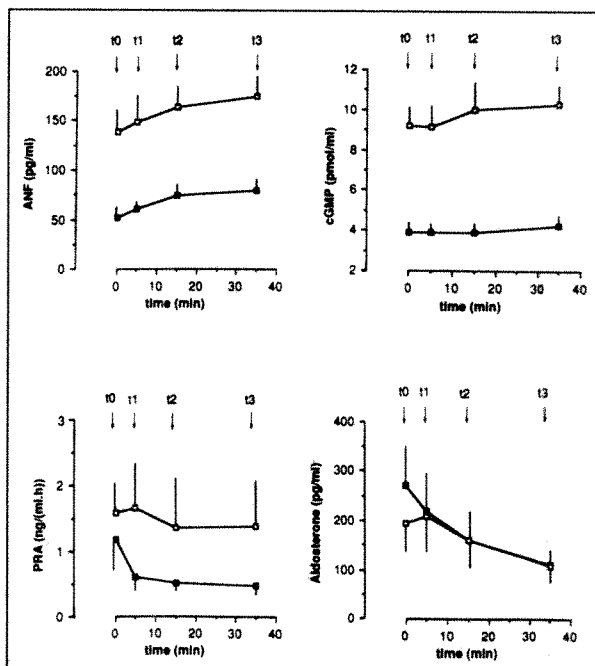


FIGURE 2. Time course of plasma atrial natriuretic factor (ANF), renin-activity (PRA), cyclic guanosine monophosphate (cGMP) and aldosterone before (t0), during (t0-t1 and t1-t2) and after (t3) an intravenous sodium load in 2 groups of heart-transplant recipients (open squares) and control patients investigated for a chest pain syndrome (closed squares). Changes with time were significant for aldosterone in both groups ($p < 0.01$) and for ANF in the control group ($p < 0.05$). Differences between groups were significant for ANF and cGMP ($p < 0.01$).

were not significantly different in both groups (Table III), cannot be responsible for the increase of plasma ANF levels observed in the transplanted patients. Therefore, other factors should be implicated. Two appear to be essential. First, atrial dimensions and/or atrial stretch have been considered to be the principal determinants controlling the release of ANF.^{14,15} In this study, right and left atrial areas were significantly correlated with plasma ANF concentration when data obtained in both groups were pooled. Moreover, since the areas of both atria were significantly greater in the group of heart-transplant recipients (Table IV), which could be explained in part by the presence of a cardiac remnant of the recipient, this parameter may have influenced the level of plasma ANF. The estimates of left atrial wall stress of all the patients were significantly correlated with plasma ANF and were significantly higher in the heart-transplant group. Similar results were not found for the right atrium, perhaps because we have used a relatively rough estimate of atrial wall stress that does not take into account the volume, the geometry and the wall thickness of the atria. A second reason for high plasma ANF levels in heart-transplant recipients may be their moderate renal insufficiency. Plasma creatinine was significantly higher in these patients and plasma ANF correlated with plasma creatinine when the data obtained in both groups were pooled. This suggests that the high plasma ANF levels of heart-transplant recipients were, in part, due to the lower renal catabolism of ANF associated with renal failure, which can be attributed to the treatment by cyclosporine.⁸

The role of cardiac denervation by itself on ANF secretion also had to be considered. We have previously reported high plasma ANF levels in patients with cardiac autonomic dysfunction such as end-stage uremic patients¹⁰ or insulin-dependent diabetic patients.¹⁶ Moreover, it has been suggested that cardiac innervation could play a role in modulating ANF secretion.^{17,18} Heart-transplant recipients exhibit symptoms of cardiac vagal denervation,⁹ which was probably responsible for the increased heart rate of the patients in this study. However, on the basis of our data, the role of cardiac denervation by itself on ANF secretion remains hypothetical.

In response to the saline load, plasma ANF increased during the infusion but did not decrease in parallel with atrial pressure at the last period in the control group. Danamberg et al,¹⁹ who observed the same results in healthy patients, hypothesized that receptors outside the atrium responded to the increase in total body salt or water by initiating neural or hormonal signals to the atrium, causing ANF secretion. According to this hypothesis, denervation of the heart transplant could explain that the increase in plasma ANF in the transplanted patients did not reach the level of significance during and after saline infusion. Alternatively, the hypothesis that the blunted ANF secretion in response to the sodium load in heart-transplant recipients could be related to their high basal plasma ANF levels is not

likely because stimulation of ANF release has been reported to occur in patients with chronic renal failure²⁰ or mitral stenosis,²¹ whose plasma ANF levels are also high.

The hemodynamic response to the sodium load during the period of saline infusion was characterized in both groups by the increase in atrial pressures, which in turn produced an increase in cardiac index without change in heart rate. This increase of cardiac index was associated with an elevation of pulmonary artery pressure without change in pulmonary vascular resistances. However, the consequences of the saline infusion on the systemic circulation were not identical in both groups. Mean arterial pressure increased slightly despite the decrease of systemic vascular resistances in heart-transplant recipients, whereas it was not modified in control patients. The phase of restoration after the end of the perfusion also appears to be different in both groups. In control patients, most of the hemodynamic parameters returned to normal values, whereas in heart-transplant recipients mean arterial pressure, pulmonary artery pressure and pulmonary wedge pressure remained elevated in comparison with their control values. This impaired vascular reactivity in transplanted patients could result from the persistence of vascular lesions independent of their initial cardiopathy. Alternatively, the sluggish response of plasma ANF in this group could be implicated in the nonreturn to basal values of the hemodynamic parameters.

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Improved Prediction of Left Ventricular Mass by Regression Analysis of Body Surface Potential Maps

Fred Kornreich, MD, PhD, Terrence J. Montague, MD, Gerard van Herpen, MD, PhD, Pentti M. Rautaharju, MD, PhD, Philippe Smets, MD, PhD, and Michèle Dramaix, MSc

Electrocardiographic left ventricular (LV) hypertrophy involving ST-T abnormalities, in addition to high QRS voltages, is associated with increased risk of cardiovascular disease mortality. Unfortunately, conventional electrocardiographic criteria have limited utility in the quantitative assessment of LV hypertrophy. Body surface potential maps, which contain diagnostic information not present in commonly used lead systems, were recorded from 117 thoracic sites and 3 limb electrodes in 72 normal subjects and 84 patients with LV hypertrophy. Multiple regression analysis was performed separately for 54 women and 102 men on 120-lead data, using as features instantaneous voltages on time-normalized P, PR, QRS and ST-T waveforms. Leads and features for optimal prediction of echocardiographically determined LV mass were selected. A total of 6 features from 3 torso sites in men, and from the same 3 sites plus 2 others in women, yielded correlations between echocardiographic and electrocardiographic estimates of LV mass of 0.89 and 0.88, respectively. The standard errors of the estimate (SEE), or average errors in predicting LV mass from the regression equations, were 31 and 22 g, respectively. The single most potent predictor in both sexes was a mid-QRS voltage measured on a lead positioned 10 cm below V₁; QRS duration, late QRS and early-to-mid T-wave amplitudes recorded in the lower left flank contributed significantly to the performance of both regression models. The optimal electrode sites for electrocardiographic prediction of LV mass were outside the conventional lead locations. In comparison, regres-

sion analysis on the standard 12-lead electrocardiogram in the same population produced a correlation of 0.76 in men and 0.75 in women; the SEE were 48 and 35 g, respectively. The Sokolow-Lyon criterion and the Romhilt-Estes point score yielded correlations of 0.57 and 0.69, respectively, in men and 0.51 and 0.67 in women. Substantial improvement in predicting LV mass from electrocardiographic measurements can be achieved by appropriate selection of a limited, practical subset of electrode positions from body surface potential maps.

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Left ventricular (LV) hypertrophy is associated with increased risk of cardiovascular mortality, particularly when electrocardiographic abnormalities include ST-T changes in addition to high QRS voltages.¹⁻³ Unfortunately, conventional electrocardiographic criteria, which are primarily aimed at recognizing the presence or absence of LV hypertrophy, have a low sensitivity and limited utility in the quantitative assessment of LV hypertrophy, for instance in comparison with echocardiographic determination of LV mass.⁴ A recent study, using an electrocardiographic estimate of LV mass on a continuous scale, indicated a substantial improvement in identifying persons at increased risk for cardiovascular mortality over conventional, dichotomous electrocardiographic criteria for LV hypertrophy; moreover, relatively high levels of correlation (0.82 for men and 0.63 for women) between electrocardiographic and echocardiographic estimates for LV mass were also reported.⁵

Body surface potential maps contain diagnostic information not readily available from standard electrocardiographic leads using conventional diagnostic criteria in a variety of cardiac conditions, including LV hypertrophy. This was demonstrated by Holt et al,⁶ who achieved a correlation as high as 0.92 between electrocardiographically and angiographically determined LV mass. However, their statistical model based on a 12-dipole model computed from QRS amplitudes from 126 recording sites is relatively complex for standard clinical applications.

In a previous study,⁷ we attempted to determine to what degree the sensitivity of detection of LV hypertrophy could be improved with multivariate analysis of

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TABLE I Multiple Regression Analysis from 120-Lead Data in 54 Women and 102 Men

Women			Men		
Variable	Reg Coef	Corr Coef	Variable	Reg Coef	Corr Coef
L 24 QRS 10	-0.06	-0.71	L24 QRS 10	-0.04	-0.74
L 103 QRS 8	-0.07	-0.47	L 86 STT 11	-0.16	-0.72
QRS duration	2.18	0.42	L 79 QRS 18	0.45	-0.54
L 79 QRS 18	0.30	-0.44	P duration	0.86	0.53
L 86 STT 11	-0.11	-0.59	QRS duration	0.81	0.55
L 16 STT 1	-0.36	0.32	L 86 P 7	-0.37	-0.37
Constant = -13.50			Constant = 33.27		

The lead numbers correspond to the recording sites of the electrocardiographic signals selected by multiple regression analysis on 120-lead data (Figure 1).

The number following the name of the waveform identifies the instantaneous measurement on that waveform, namely 8, 18 and 18 voltages for P, PR, QRS, and ST-T waveforms, respectively, in addition to the durations of these waveforms (see text).

Corr Coef = (univariate) correlation coefficient; L = lead; Reg Coef = regression coefficient.

body surface potential map data while retaining a high level of specificity. Using a 120-lead data file of 173 normal subjects and 122 patients with pure LV hypertrophy, we identified 6 electrocardiographic features from 5 torso locations that yielded a 94% sensitivity with a 97% specificity. While this represents a promising improvement in the diagnosis of LV hypertrophy over criteria from the 12-lead electrocardiogram, no assessment was performed to determine how well the severity of LV hypertrophy can be quantified using statistical models for estimation of LV mass. The primary potential utility of such models lies in attempts to quantify progression and regression of LV hypertrophy in clinical intervention studies. In the present investigation we used the echocardiogram as an electrocardiogram-independent standard for a regression model using body surface potential map data from 156 subjects to derive a

limited, practical subset of electrocardiographic data for optimal estimation of LV mass.

METHODS

Study population: We retrospectively studied 156 subjects for whom 120-lead data and good quality M-mode echocardiograms were available and recorded within a mean of 2 days of each other: 72 were normal subjects and 84 were patients with LV hypertrophy. The normal group consisted of 26 women ranging in age from 24 to 70 years (mean 42) and 46 men ranging in age from 25 to 69 years (mean 45), with no evidence of heart disease by history, physical examination, chest x-ray and M-mode echocardiography. Patients were 14 to 71 years old (mean 48); 28 were women and 56 men. The presence of LV hypertrophy was assessed by M-mode echocardiograms; the diagnosis was further substantiated by cardiac catheterization with ventriculography, radionuclide angiography, chest radiographs, cardiac surgery or a combination of these: 36 patients had aortic stenosis, 31 patients had sustained hypertension (>150/90 mm Hg) and 17 patients had coronary artery disease.

Echocardiography: M-mode echocardiograms were performed with patients in the left lateral decubitus position. All measurements of the LV cavity, ventricular septum and LV posterior wall were obtained at the minor dimension of the left ventricle; the measurements were performed independently by two observers, using the Penn convention⁸ to determine LV mass: the latter ranged from 94 to 346 g in women and from 126 to 527 g in men; the upper normal limits for both sexes in the study population were 179 and 221 g, respectively. These values represent approximately the normal mean + 2 standard deviations in women (mean 137 g, standard deviation 20 g) and in men (mean 173 g, standard

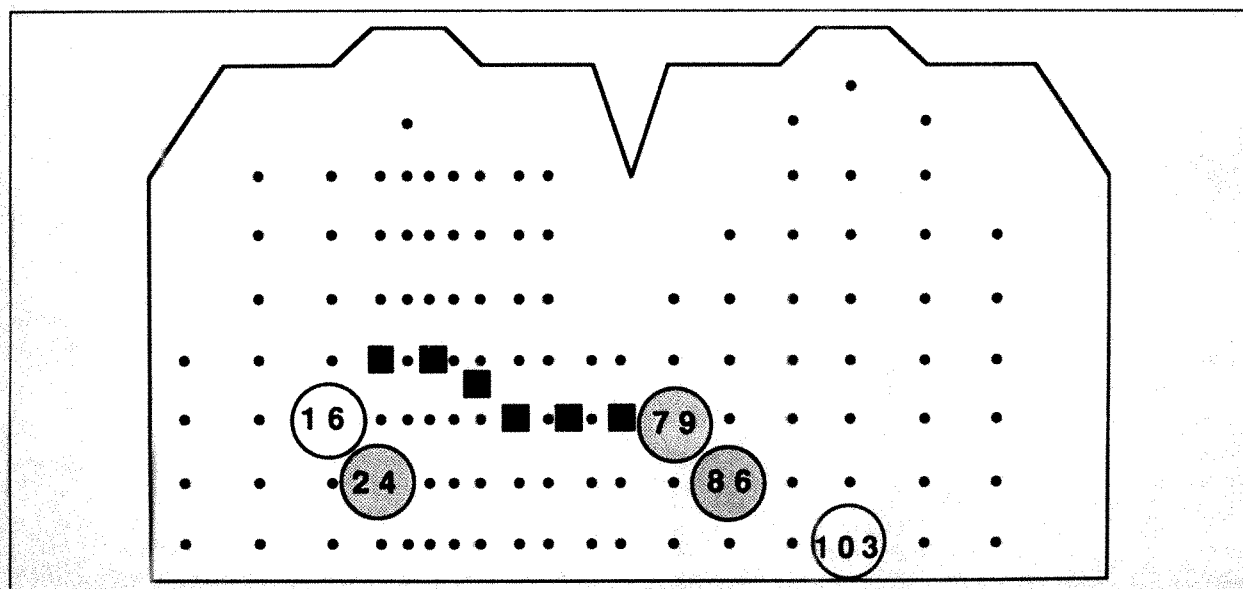


FIGURE 1. Unfolded torso with 117 recording sites. The left of each map represents the anterior torso and the right represents the back. The black squares correspond to the V_1 through V_6 standard electrode positions. The circles indicate specific leads selected in the regression analysis: leads 24, 79 and 86 (shaded circles) provided measurements to the regression equation for men and leads 16 and 103, additional measurements for women (Table I).

deviation 23 g) and were used earlier⁷ as thresholds for classification purposes.

Body surface potential mapping: Electrocardiographic signals were recorded simultaneously on digital tape from 117 torso and 3 limb electrode sites in each subject and digitized at 500 samples/s with Wilson's central terminal as reference potential. Tracing quality was monitored visually during the recording; later the stored data were processed by performing selective averaging and again carefully edited. Details of the procedure have been reported previously.⁹ All measurements were performed with the TP segment as baseline, and common time instants for P onset, P offset, QRS onset, QRS offset and T offset were derived from superimposed Frank X, Y and Z leads. We then time-normalized separately the P wave, the PR segment, the QRS waveform and the ST-T waveform and represented them by 25, 25, 70 and 180 points, respectively.

Feature extraction and regression analysis: We used instantaneous voltage measurements obtained by sampling the time-normalized waveforms at equal intervals; this resulted in 8, 8, 18 and 18 samples for P wave, PR segment, QRS and ST-T waveforms, respectively, i.e. 52×120 data/subject. Added to these variables were P, PR, QRS and ST-T durations measured before time-normalization. Stepwise multiple linear regression

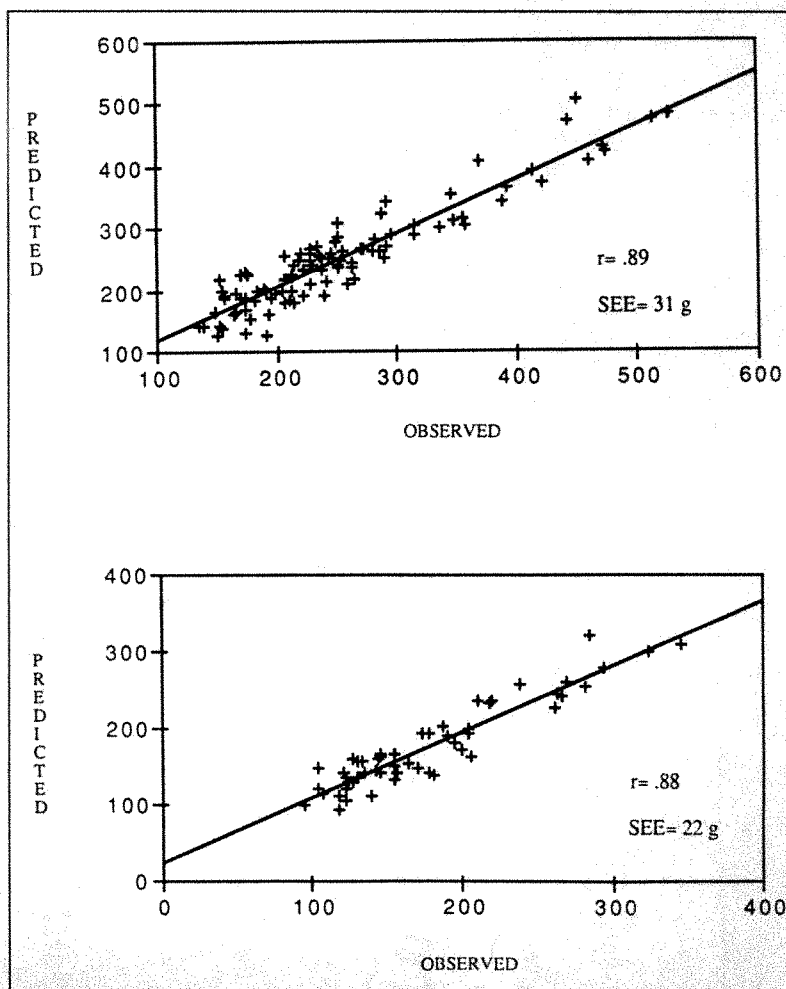
TABLE II Multiple Regression Analysis from 12-Lead Data in 54 Women and 102 Men

Women			Men		
Variable	Reg Coef	Corr Coef	Variable	Reg Coef	Corr Coef
V 6 STT 11	-0.20	-0.58	V 6 STT 11	-0.14	-0.63
I QRS 10	0.04	0.46	V1 QRS 9	-0.02	-0.56
QRS duration	0.60	0.42	V6 STT 3	0.29	-0.39
V 6 STT 3	0.70	-0.39	QRS duration	1.42	0.55
P duration	1.35	0.44	P duration	0.79	0.53
V 5 QRS 18	-0.22	-0.41	I QRS 10	0.02	0.51
Constant = -17.95			Constant = -30.81		

The number following the name of the waveform identifies the instantaneous measurement on that waveform (see text). Abbreviations as in Table I.

analysis was performed using a program of the Biomedical Program library¹⁰; using electrocardiographic measurements from 120 leads as continuous independent variables for estimating echocardiographic LV mass, separate regression equations were computed for women and for men. Similarly, prediction formulas were derived separately for women and for men from the 12-lead electrocardiogram. For comparative purposes we also tested regression variables extracted from the con-

FIGURE 2. Relation between observed echocardiographic LV mass (*abscissa*) and LV mass predicted from 120-lead data (*ordinate*). Separate plots depict the relation in men (*top*) and in women (*bottom*). r = the correlation coefficient; SEE = standard error of the estimate.



ventional electrocardiogram and recently reported by Casale et al¹¹ and by Rautaharju et al.⁵

RESULTS

Correlation between left ventricular mass and 120-lead data: Table I lists the regression variables and their coefficients for both sexes. The electrode positions from which the listed variables originate are shown in Figure 1; 3 recording sites are common to men and to women (leads 24, 79 and 86) and 2 additional sites are selected for women only (leads 16 and 103). Figure 2 shows echocardiographic LV mass plotted against LV mass computed from map data. The correlation between echocardiographic and electrocardiographic estimates of LV mass was practically identical in both sexes (0.88 versus 0.89); the standard error of the estimate (SEE) was 22 g for women and 31 g for men. The single most powerful, common predictor both in men and in women is a mid-QRS voltage measured on a lead positioned 10 cm below V_1 (lead 24). Univariate correlations between single variables and LV mass show important sex-related differences: QRS duration is selected in both regression models but correlates better with LV mass in men ($r = 0.55$ vs $r = 0.42$); also, while men require additional P-wave information (P duration and terminal P voltage in lead 86), women use a mid-QRS voltage in the lower back and a very early ST voltage in the vicinity of

V_1 (lead 16). Early-to-mid T-wave voltages in the lower left flank also contribute significantly to the overall performance of the regression model and correlate better with observed LV mass in men ($r = -0.72$) than in women ($r = -0.59$); the same holds for a late QRS measurement, corresponding to the J-point, in the same area (lead 79).

Correlation between left ventricular mass and the 12-lead electrocardiogram: Table II lists the regression variables derived from the conventional electrocardiogram for both sexes. Again, similar multiple correlation coefficients are obtained, 0.75 for women and 0.76 for men; the corresponding SEE are 35 and 48 g, respectively. Figure 3 shows echocardiographic LV mass plotted against LV mass computed from 12-lead data. The best predictor in both groups is an early-to-mid T voltage in V_6 ; other common measurements are P and QRS durations, a mid-QRS voltage in lead I and an early ST voltage in V_6 . Important sex-related differences are also present: QRS and P durations are better correlated to LV mass in men ($r = 0.55$ and $r = 0.53$) than in women ($r = 0.42$ and $r = 0.44$) while V_1 QRS 9/18, which corresponds roughly to the S wave, is a good predictor in men only ($r = -0.56$).

Using the criteria reported by Casale et al¹¹ (RaVL, SV3, TV1, QRS duration and P wave terminal forces in V_1) for estimating LV mass in our groups yielded $r =$

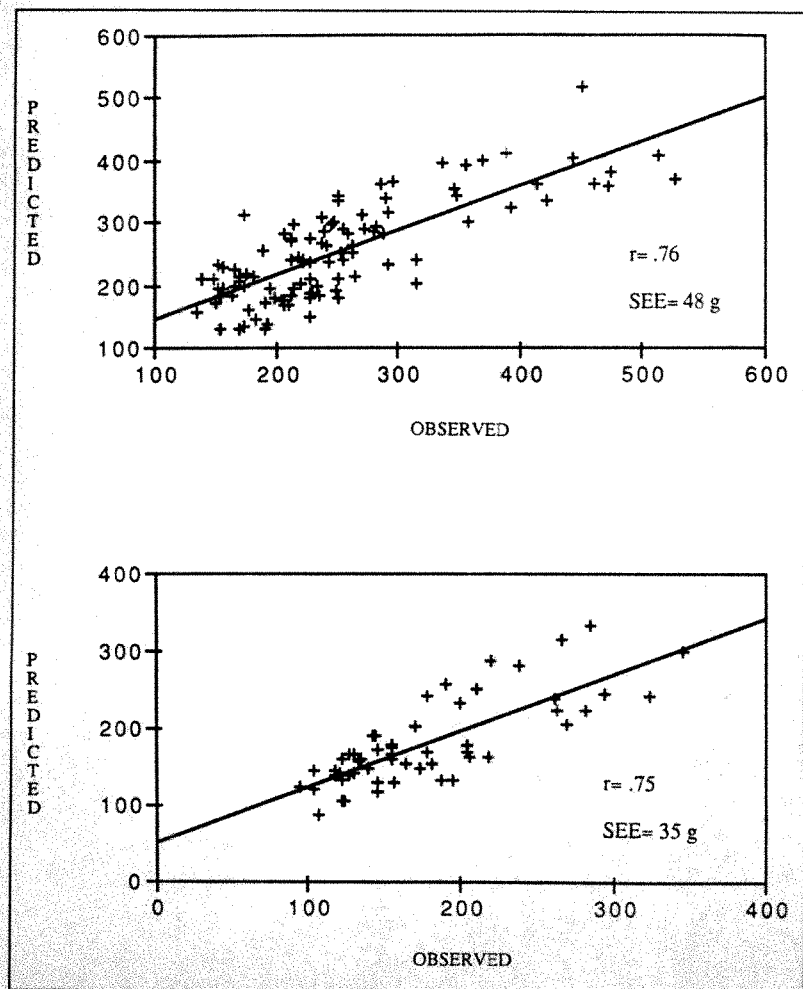


FIGURE 3. Relation between observed echocardiographic LV mass (*abscissa*) and LV mass predicted from the 12-lead standard electrocardiogram (*ordinate*). Separate plots depict the relation in men (*top*) and in women (*bottom*). Abbreviations as in Figure 2.

0.67 in women (SEE = 38 g) and $r = 0.71$ in men (SEE = 51 g). We also implemented the regression equations suggested by Rautaharju et al⁵ in our data and obtained $r = 0.70$ in women (SEE = 37 g) and $r = 0.72$ in men (SEE = 50 g).

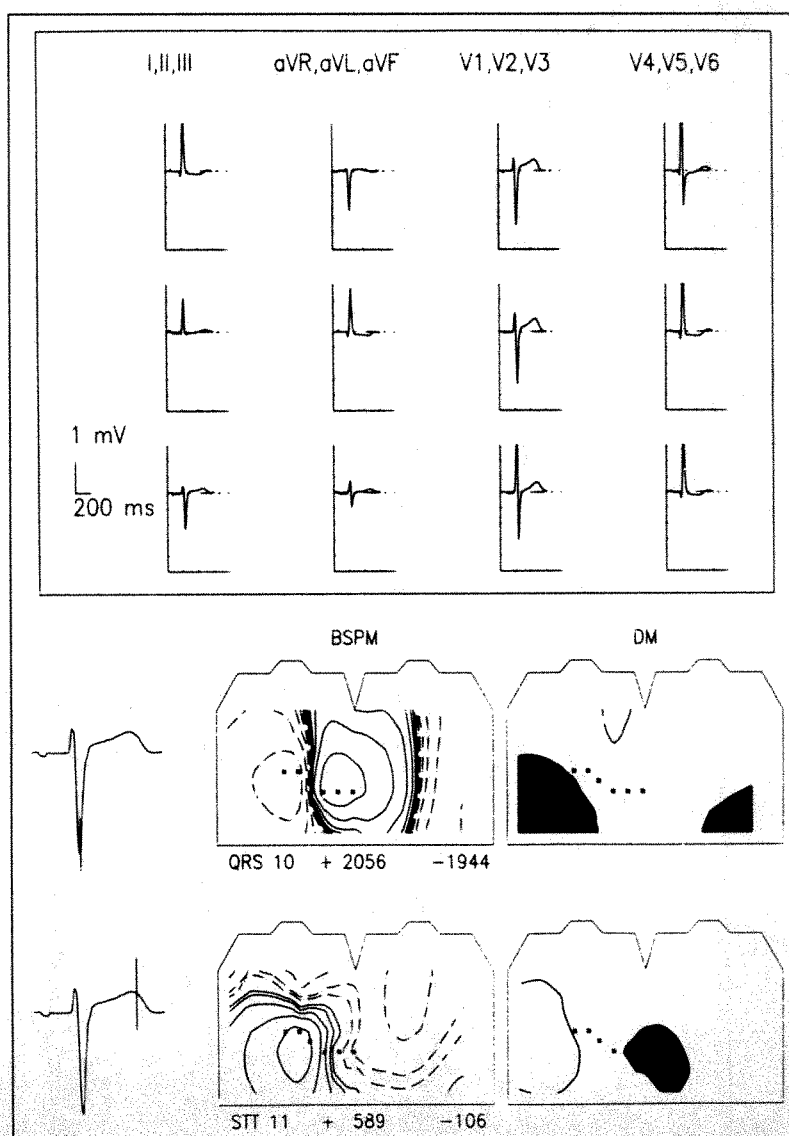
DISCUSSION

Optimal lead sites and measurements for prediction of left ventricular mass: The best lead positions for the prediction of LV mass by electrocardiographic measurements were outside the conventional lead locations in both sexes: men required measurements from 3 electrodes and women from 2 additional electrode sites. Interestingly, these positions are identical to, or in the immediate vicinity of, those reported for optimal classification purposes in a recent investigation on a population from which the present study group originates.⁷ Several variables, selected as good discriminators, are also entered in the regression equations, albeit not in the same order (e.g., P duration, which was the single best classifier separating normotrophic from hypertrophic subjects shows up at step 4 in the regression model for men and

not at all in the model for women; on the other hand, QRS duration, which was only a modest classifier, is a good predictor of LV mass). A possible explanation is that prolonged P duration mainly identifies severe LV hypertrophy while the duration of depolarization is more directly proportional to the amount of myocardium. These discrepancies result from the essential differences between discriminant and regression analyses: indeed, discriminant analysis reduces several correlated measurements for each individual to a single weighted composite score and determines a cutting point that minimizes errors of misclassification while multiple regression analysis computes a quantitative relation between a single dependent variable (e.g., LV mass) and several independent variables or predictors (e.g., voltages and durations) on a continuous scale without aiming at a clear demarcation line.

Figures 4 and 5 illustrate the better and more consistent predictions achieved with map data over the 12-lead electrocardiogram. Figure 4 represents a male patient with aortic stenosis and echocardiographic LV mass of 269 g. The Sokolow-Lyon voltage¹² reached 41

FIGURE 4. Top, the 12-lead electrocardiogram from a patient with aortic stenosis. Bottom, body surface potential maps (BSPM) and discriminant maps (DM) from the same patients at instants indicated at the left of the maps on a reference lead (at 10/18 QRS and 11/18 ST-T). The solid contour lines in the maps indicate positive voltages and the dashed lines negative voltages. Minimum and maximum voltages are indicated below each map. Discriminant maps are obtained by subtracting from each map the normal group mean voltage and by dividing the resulting difference by the standard deviation computed from the normal group; the blackened areas enclose negative voltages exceeding normal values by at least 2 standard deviations; the solid lines correspond to excessive positive voltages.



mm and the Romhilt-Estes score¹³ yielded 7 points. P duration was 116 ms and QRS duration, 104 ms. Excessive negative voltages were present in the lower right anterior chest at mid-QRS and in the left flank at the peak of the T wave; these patterns, typical of LV hypertrophy, were described in an earlier report.¹⁴ The regression model computed from map data predicted LV mass at 258 g while the prediction from the 12-lead electrocardiogram produced 311 g. The male patient shown in Figure 5 had severe hypertension and coronary artery disease; echocardiographic LV mass was 264 g. The Sokolow-Lyon voltage equaled 29 mm and the Romhilt-Estes point score was 4. P and QRS durations were 106 ms and 88 ms, respectively. Multiple regression analysis from maps and from the 12-lead electrocardiogram yielded predicted LV masses of, respectively, 245 and 202 g. Here too, map patterns typical in time and in location of LV hypertrophy and unsampled by standard precordial lead positions were observed.

Relation to previous work: Numerous criteria based on the standard electrocardiogram have been proposed to separate normal subjects from patients with LV hypertrophy (i.e., to indicate the presence or absence of LV hypertrophy). Much less emphasis, however, has been placed on the quantitative relation between the severity of LV hypertrophy and conventional electrocardiographic criteria. Most attempts at correlating echocardiographic or angiographic LV mass with electrocardiographic measurements have used the Sokolow-Lyon index and the Romhilt-Estes point score, obtaining correlation coefficients ranging from 0.36 to 0.73 for the former and 0.34 to 0.72 for the latter. Recently, Casale et al¹¹ developed sex-specific criteria for LV hypertrophy and reported correlations between these criteria and LV mass at autopsy of 0.62 in men and 0.70 in women. Rautaharju et al,⁵ investigating the prognostic value of LV mass estimated from an electrocardiographic model for predicting the risk of cardio-

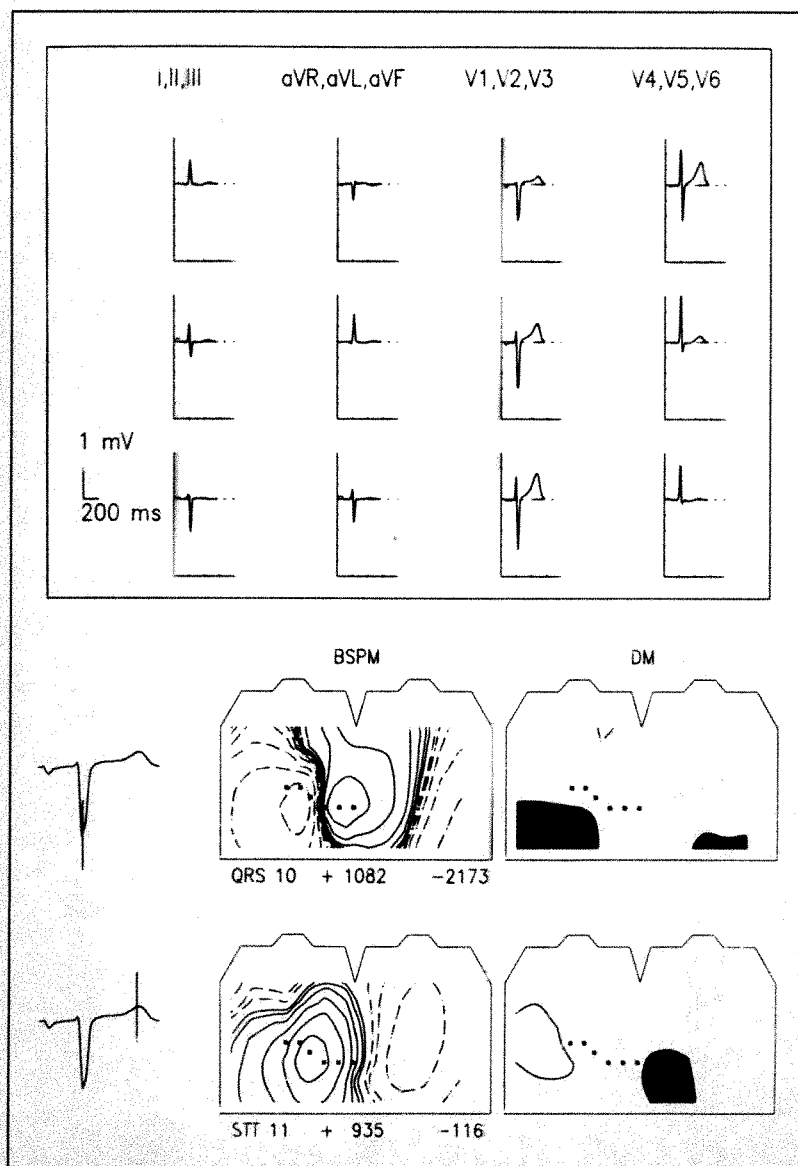


FIGURE 5. Patient with severe hypertension and coronary artery disease. Abbreviations as in Figure 4.

vascular disease mortality, computed regression equations for different race-sex groups and produced fairly high levels of correlation between echocardiographic and electrocardiographic estimates for LV mass index (g/m^2) (0.82 for men and 0.63 for women).

The diagnostic yield of the electrocardiogram could be further enhanced with the use of multiple lead data. Holt et al,⁶ using tracings from 126 body surface sites and deriving 12 dipole electrocardiograms, achieved a correlation of 0.92 between angiographically determined LV mass and the multiple dipole model. In a later study, Dunn et al¹⁵ compared the performance of the 12-lead electrocardiogram, Frank's XYZ leads and the multiple dipole model and reported correlation coefficients of 0.61, 0.78 and 0.89, respectively. Recently, Yamaki et al¹⁶ evaluated body surface map features during QRS for accuracy in estimating LV wall thickness and achieved a correlation of 0.73, which compared favorably with the Sokolow-Lyon voltage (0.44) and the Romhilt-Estes score (0.59). In the present study, we combined P, QRS and ST-T voltages from map data as well as durations to achieve correlations of 0.89 in men and 0.88 in women; corresponding coefficients for the 12-lead electrocardiogram were 0.76 and 0.75. In the same population the correlation between the Sokolow-Lyon voltage and LV mass was 0.57 in men and 0.51 in women; the Romhilt-Estes point score yielded correlation coefficients of 0.69 and 0.67, respectively. Interestingly, the results achieved in the present population with the measurements proposed by Casale et al¹¹ and by Rautaharju et al⁵ were very similar (roughly 0.70 for both sexes) and comparable to those obtained with the point score, suggesting the existence of a large variety of regression models derived from the standard electrocardiogram with only slightly different performances.

Study limitations: The first limitation deals with the assessment of LV hypertrophy. Numerous studies have compared angiographic and echocardiographic measurements with autopsy findings for the prediction of LV mass. In the present study, LV mass was computed from M-mode echocardiograms according to the Penn convention. Although these measurements are themselves estimates, they were found acceptably accurate; for instance, Devereux and Reichek⁸ reported a correlation of 0.96 between echocardiographic and postmortem LV mass. It is also possible that 2-dimensional echocardiograms may further improve estimation of LV size. The technical quality of echocardiographic tracings is indeed of great importance since small errors in measuring thicknesses translate into large errors for total LV mass. Another source of error is the variability resulting from beat-to-beat and day-to-day variations in both the electrocardiographic and the echocardiographic data. In the present study, the SEE, which may be interpreted as a sort of average error in predicting LV mass from the regression equation, was 31 g in men and 22 g in women; in that respect it is interesting to note that when echocardiographic recordings from the present investigation were measured by 2 experienced echocardiographers (TM and GvH), the difference in calculated

LV mass ranged from 0 to 49 g (mean 26 g); no systematic bias was observed. Ideally, LV mass should be estimated in relation to body surface area; however, because of the retrospective character of the present study, body surface area was not available for each subject.

A second limitation is the inadequacy of the regression model in atrial fibrillation because of the inclusion of P data in the analysis. Performing multiple regression analysis from 120-lead data in men without P-wave measurements resulted in a multiple correlation coefficient of 0.86 (from 0.88 with P data) and a SEE = 34 g (from 31 g); an early ST measurement in lead 16 and a late T voltage in lead 86 were substituted for the P data in the regression model (Table I).

Other limitations are patient selection and sample size. Only subjects with clear-cut LV hypertrophy were included in the study population. Most patients had either aortic valve disease or severe hypertension; it is therefore quite possible that the prediction model may be found less adequate in milder forms of LV hypertrophy. Also, the marginal sample size did not allow stratification by age or meaningful breakdown in training and testing sets. The main point, however, is that quantitative estimation of LV mass from body surface potential maps was clearly superior to that achieved with the standard 12-lead electrocardiogram, given the same limitations for both methods.

Clinical implications: The electrocardiogram is the easiest, least expensive and most widely used noninvasive method for detecting the presence of LV hypertrophy; in contrast with the echocardiogram, it can be performed on all patients and there are no important technical constraints. The present study addressed the quantification of LV hypertrophy rather than the mere recognition of the condition; it identified a limited number of recording sites (3 for men and the same 3 plus 2 others for women) from which simple voltage measurements, in addition to P and QRS durations, could be computed for optimal estimation of LV mass. These lead positions were outside the conventional electrocardiographic lead locations, namely in the lower right anterior chest and in the left flank and lower back. To fully establish the clinical usefulness of the present results for estimating LV mass, larger and more diversified groups of subjects need to be explored: it is indeed imperative to have a stable and reliable model for predicting LV mass before it can be used to follow the evolution of LV hypertrophy and the possible effects of therapy on cardiac size.

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Noninvasive Estimation of Right Atrial Pressure from the Inspiratory Collapse of the Inferior Vena Cava

Barbara J. Kircher, MD, Ronald B. Himelman, MD, and Nelson B. Schiller, MD

To evaluate a simple noninvasive means of estimating right atrial (RA) pressure, the respiratory motion of the inferior vena cava (IVC) was analyzed by 2-dimensional echocardiography in 83 patients. Expiratory and inspiratory IVC diameters and percent collapse (caval index) were measured in subcostal views within 2 cm of the right atrium. Parameters were correlated with RA pressure by flotation catheter within 24 hours of the echocardiogram (38 were simultaneous). Correlations between RA pressure (range 0 to 28 mm Hg), expiratory and inspiratory diameters and caval index were 0.48, 0.71 and 0.75, respectively. Of 48 patients with caval indexes <50%, 41 (89%) had RA pressure ≥ 10 mm Hg (mean \pm standard deviation, 15 ± 6), while 30 of 35 patients (86%) with caval indexes $\geq 50\%$ had RA pressure < 10 mm Hg (mean 6 ± 5). Sensitivity and specificity for discrimination of RA pressure \geq or < 10 mm Hg were maximized at the 50% level of collapse. Thus, IVC respiratory collapse on echocardiography is easily imaged and can be used to estimate RA pressure. A caval index $\geq 50\%$ indicates RA pressure < 10 mm Hg, and caval indexes $< 50\%$ indicate RA pressure ≥ 10 mm Hg.

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Knowledge of right atrial (RA) pressure is of clinical value because it reflects right-sided cardiac hemodynamics and central blood volume. It is also useful in the noninvasive evaluation of pulmonary pressures. Doppler echocardiography provides a method to estimate pulmonary pressures.^{1,2} Peak pulmonary systolic pressure is estimated by summing the peak pressure calculated from the Doppler velocity of tricuspid regurgitation ($\Delta P = 4V^2$) and the RA pressure. An accurate mean RA pressure will add precision to these pulmonary pressure calculations. Studies have confirmed the relation of the inferior vena cava (IVC) size and behavior to right-sided cardiac hemodynamics and central blood volume.³⁻⁷ In this study, we sought to determine the efficacy of inspiratory collapse of the IVC on 2-dimensional echocardiography as a simplified guide to RA pressure.

METHODS

Analysis of records of right-sided cardiac catheterizations at our institution from January 1985 to September 1987 revealed 113 patients who had an echocardiogram within 24 hours of hemodynamic evaluation. There were 30 patients excluded due to presence of mechanical ventilation (10), or technically inadequate or absent IVC imaging, leaving 83 study patients. Of these, 38 had an echocardiogram and right-sided cardiac hemodynamics performed during the same hour ("simultaneous"). The right-sided cardiac catheterization was performed using flow-directed pulmonary artery catheters in intensive care units (66 patients) or in the cardiac catheterization laboratory (17 patients). Mean RA pressure measurements were obtained from monitor-produced strips by trained nursing staff in the intensive care units and by cardiologists in the catheterization laboratory. Charts were reviewed for mean RA pressure, and presence or absence of mechanical ventilation.

Measurements of IVC diameters were performed by 2 independent observers from long-axis 2-dimensional subxiphoid views, with the patient in a supine to 30° upright position. Following long established routine laboratory practice, alert patients were asked to inspire without performing a Valsalva maneuver during imaging of the IVC. If minimal or no collapse was observed, patients would then be asked to "sniff" several times. The transducer was angled laterally and medially to record maximum IVC size. All measurements were made within 2 cm of the RA origin of the IVC. Using movement of the diaphragm as a guide to inspiration, the

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minimum inspiratory and the maximum expiratory diameters of the IVC were determined after frame-by-frame analysis. Diameters were measured by calipers using the trailing edge to leading edge technique. The "caval respiratory index" was defined as the percent decrease in diameter of the IVC with inspiration (Figures 1 and 2).

Data analysis: Results are presented as mean \pm standard deviation. Correlations of RA pressure with IVC diameters and the caval respiratory index were determined with least-squares linear regression analysis. Mean values between groups were compared by the paired *t* test. The null hypothesis was rejected at the 5% probability level. Sensitivity, specificity and predictive accuracy were calculated in standard fashion.⁸ Interobserver variability was defined as the average percent difference in measurement values between the 2 observers.

RESULTS

The study included 83 patients who had echocardiography of the IVC performed within 24 hours of right-

sided cardiac catheterization, including 38 with simultaneous evaluations. There were 43 men and 40 women, with an average age of 61 years (range 23 to 87). Interobserver variability for echocardiographic measurements was 8%.

The mean RA pressure averaged 11 ± 7 mm Hg (range 0 to 28) for all patients, and in the subgroup of simultaneous patients (Table I). There were no significant differences between all patients and the group of simultaneous patients.

Although the end-expiratory diameter of the IVC did not correlate closely with RA pressure ($r = 0.48$), there was a better correlation of the end-inspiratory diameter and RA pressure ($r = 0.71$, standard error of the estimate [SEE] = 4.8, Figure 3). The correlation between RA pressure and the caval respiratory index was $r = 0.75$ (SEE = 4.5, Figure 4). This correlation did not improve when only simultaneous patients were analyzed ($r = 0.73$, SEE = 4.0).

All those patients having respiratory caval indexes $\leq 20\%$ had RA pressures above 10 mm Hg. Of 48 pa-

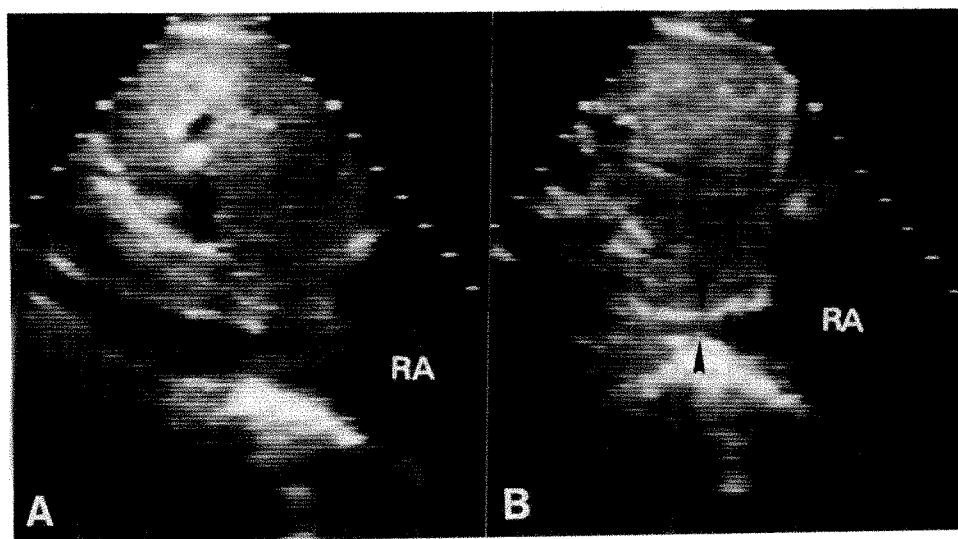


FIGURE 1. Long-axis 2-dimensional subxiphoid image of the inferior vena cava and right atrium (RA) showing end-expiratory (A) and end-inspiratory (B) phases. Arrows indicate area of collapse, measured to be $>50\%$ in this patient.

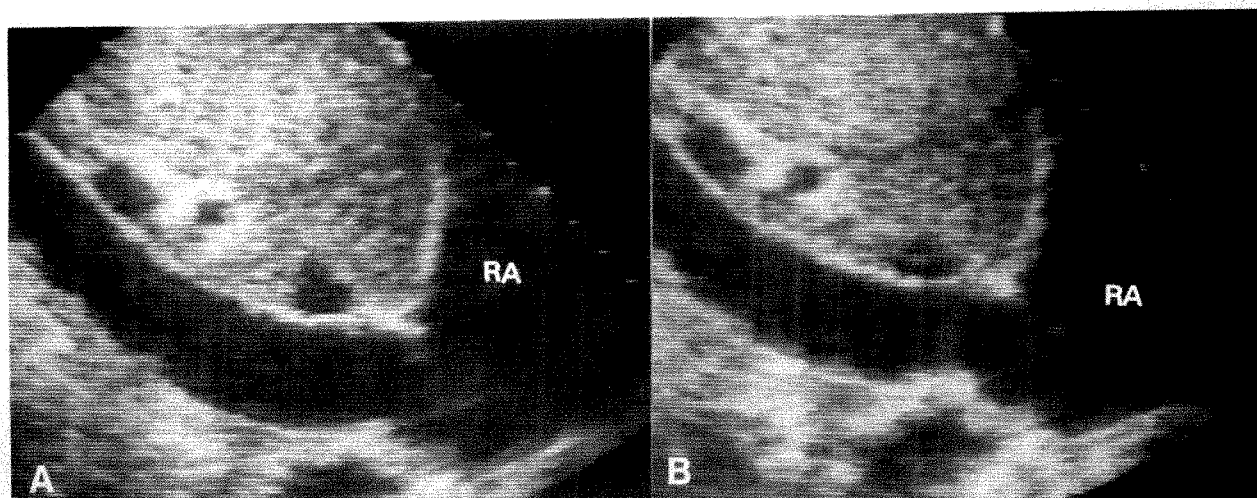


FIGURE 2. Long-axis 2-dimensional subxiphoid image of the inferior vena cava and right atrium (RA) showing end-expiratory (A) and end-inspiratory (B) phases. The IVC is plethoric and shows minimal response to respiration.

TABLE I Inferior Vena Cava Dimensions and Percent Collapse

Group	No. of Pts	Initial Diameter (cm)	Final Diameter (cm)	Percent Collapse
All	83	1.9 ± 0.5	1.2 ± 0.7	42 ± 25
Simultaneous	38	1.9 ± 0.5	1.1 ± 0.7	44 ± 26

tients who had respiratory caval indexes <50%, 47 (89%) had RA pressure ≥10 mm Hg (mean 15 ± 6 mm Hg). Of 35 patients with caval indexes ≥50%, 30 (86%) had RA pressures <10 mm Hg (mean 6 ± 5 mm Hg, $p < 0.001$). Caval dimensions and respiratory caval indexes of these patients are listed in Table II.

At various levels of IVC collapse, the sensitivity and specificity of the caval respiratory index for an RA pressure ≥10 mm Hg were determined (Table III). Sensitivity and specificity were optimized at the 50% level of collapse. At this level, the predictive accuracy for RA pressure > or <10 mm Hg was 88 and 81%, respectively.

DISCUSSION

The size and respiratory response of the IVC is known to reflect right-sided cardiac hemodynamics and

TABLE II Inferior Vena Cava Dimensions and Caval Indexes for Patients with < or ≥50% Inferior Vena Cava Respiratory Collapse

	<50% Collapse	≥50% Collapse
Initial diameter (cm)	2.1 ± 0.4* (0.7-3.0)	1.6 ± 0.5 (0.4-2.5)
Final diameter (cm)	1.6 ± 0.4* (0.6-2.6)	0.6 ± 0.4 (0.0-1.6)
Caval index (%)	24 ± 13.8*	65 ± 18.3

Ranges are in parentheses.
* $p < 0.05$ versus ≥50% group.

central blood volume. During inspiration, negative intra-pleural pressure develops, permitting increased venous return to the right heart. As flow in the IVC increases and intraluminal pressure decreases, the diameter of this highly compliant vessel decreases. Increased intraabdominal and diaphragmatic compression during inspiration may also play a role in the collapse of the IVC. This normal inspiratory collapse of the IVC is altered when flow is impeded by increased right-sided cardiac filling pressures.

Two-dimensional echocardiography provides a non-invasive, in vivo, real-time means of imaging the respiratory dynamics of the IVC. Previous attempts to esti-

FIGURE 3. Regression line of right atrial pressure versus end-inspiratory inferior vena caval diameter showing regression equation. $r = 0.71$; standard error of the estimate = 4.8 mm Hg.

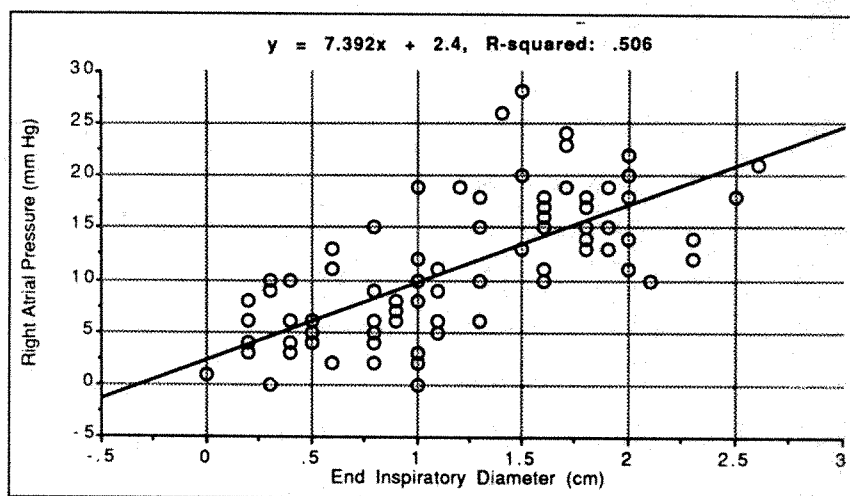


FIGURE 4. Regression line of right atrial pressure versus respiratory caval index showing regression equation and 95% confidence limits. $r = 0.75$; standard error of the estimate = 4.5 mm Hg.

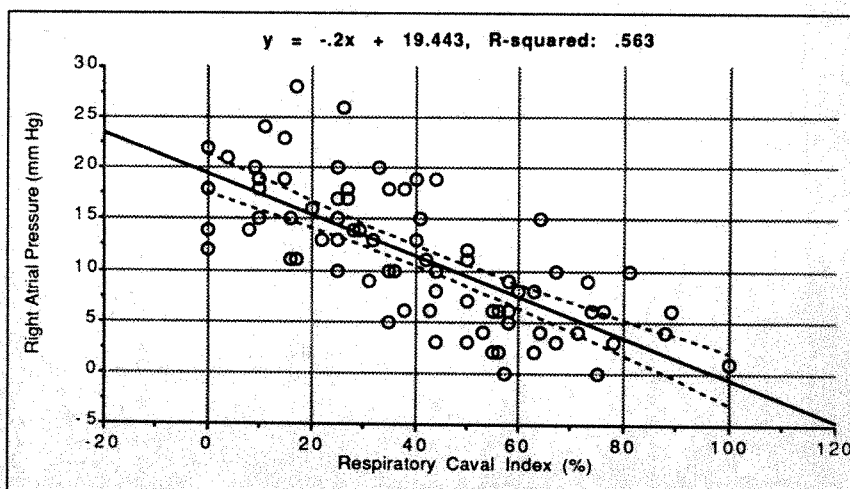


TABLE III Sensitivity and Specificity for Predicting Right Atrial Pressure ≥ 10 mm Hg with Different Percent Inferior Vena Cava Collapse

% Collapse	% Sensitivity	% Specificity
20	38	100
40	74	91
50	87	82
60	94	44
80	98	14

mate RA pressure from echocardiography of the IVC have been qualitative and have been based on M-mode images. In 50 patients, Mintz et al⁵ found RA pressure ≥ 10 mm Hg correlated with an IVC end-diastolic diameter ≥ 10 mm/m². Amano et al⁴ found a poor correlation of IVC dimension and RA pressure ($r = 0.54$), but reported a high predictive accuracy of RA pressure < 5 mm Hg for IVC end-diastolic dimension < 20 mm. Neither of these studies found a good correlation between the M-mode equivalent of the respiratory caval index and the RA pressure. In 65 patients with some form of heart disease, Moreno et al⁶ reported RA pressure correlated with the inspiratory collapse, with $r = 0.71$, similar to our result. They concluded that a collapsibility index of 40% on M-mode could separate patients with right-sided cardiac disease from those with normal right heart function.

We have shown the caval respiratory index by 2-dimensional echocardiography correlates with RA pressure. A caval respiratory index of 50% gives the highest overall sensitivity and specificity, and an acceptable predictive accuracy for separating patients with RA pressures $<$ and > 10 mm Hg. Patients with an inspiratory collapse $\geq 50\%$ tend to have RA pressures < 10 mm Hg, and those having $< 50\%$ collapse tend to have RA pressures ≥ 10 mm Hg.

Measuring the IVC from 2-dimensional images provides several advantages over M-mode measurements. Although Moreno et al showed a good correlation between 2-dimensional and M-mode measurements of the IVC in both the short ($r = 0.86$) and long axis ($r = 0.84$),⁶ it is easier to locate the site where the IVC collapses to the greatest degree from the 2-dimensional image. Errors of angle and translocation introduced by M-mode are reduced by 2-dimensional echocardiography. Since the force of the inspiratory effort may vary from patient to patient, the use of quantitative sonospirometry can improve the accuracy of the RA pressure es-

timation.³ Although this is an accurate technique, it requires additional equipment, as well as patient cooperation and inspiratory breath-holding for 5-second periods, which are not always possible in severely dyspneic patients.

Study limitations: Echocardiographic imaging and hemodynamics should preferably have been performed at the same time in all patients, since volume status can change rapidly. However, our correlation of RA pressure and respiratory caval index was not different between the entire group of patients and the simultaneous group. Positive pressure ventilation, varying force of inspiratory effort and inability of some patients to inspire deeply due to severe breathlessness, chest pain or decreased mentation are also limitations in using 2-dimensional echocardiographic IVC behavior to predict RA pressure. These problems can occasionally be alleviated by having patients "sniff" while imaging the IVC.

Clinical implications: Since the highest overall sensitivity and specificity for RA pressure was found at the 50% level of collapse in our study, we recommend using this value to differentiate normal from elevated central venous pressure. In our laboratory, when the caval respiratory index exceeds 50%, we assume that RA pressure is approximately 5 mm Hg. When the caval index is $< 50\%$, we assume that RA pressure is approximately 15 mm Hg.

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Autonomic Nervous System Activity During Myocardial Ischemia in Man Estimated by Power Spectral Analysis of Heart Period Variability

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Ambulatory patients with coronary artery disease exhibit a nearly universal increase in heart rate during episodes of ST depression.¹ The cause of the increase in heart rate presumably represents an increase in sympathetic nervous activity, a decrease in parasympathetic nervous activity, or both. The purpose of this investigation was to determine the cause of increased heart rate during ambulatory ischemic episodes using power spectral analysis of normal RR intervals. An increase in sympathetic nervous activity causes an increase in low frequency power and an increase in the low to high frequency ratio. A decrease in parasympathetic nervous activity causes a decrease in both low and high frequency power, that is, no change or a decrease in the low to high frequency ratio.

Fifteen 24-hour electrocardiographic recordings were obtained 2 to 6 months after hospitalization for either myocardial infarction ($n = 7$) or unstable angina pectoris ($n = 7$) from 14 patients (13 men, 1 woman) enrolled in the Multicenter Study of Silent Myocardial Ischemia, a prospective natural history study evaluating the predictive value of asymptomatic ST depression.² Each of the 15 tapes showed ≥ 1 episode of myocardial ischemia, defined as ≥ 1 mm ST depression that persisted for ≥ 1 minute.

Recordings were made, digitized at 128 Hz, and analyzed with Marquette 8500 recorders and 8000 scanners. For each ischemic episode, the following information was recorded: start time, stop time, maximum ST depression in mm, the integral of the ST depression from start time to stop time, the heart rate at the onset of the ischemic episode and the heart rate at the time of maximum ST depression.

The digitally sampled electrocardiographic data were transferred from the Marquette scanner to a Sun 3/160 microcomputer for power spectral analysis. Power spectra were computed on consecutive 5-minute segments of the 24-hour recording. A continuous function was derived from the normal RR intervals. This time series was sampled to obtain 1,024 equally spaced data points per segment. Intervals of noise, missed QRS com-

plexes and atrial or ventricular premature complexes were spanned by linear splining.³ Segments that required more than 20% splining were excluded from analysis. The power spectra were computed using Bartlett's procedure, in which sequential windowed segments of the normal RR interval function are transformed into the frequency domain and averaged.⁴ Power spectra were quantified by measuring the area in 2 frequency bands: 0.04 to 0.15 Hz (low frequency power) and 0.15 to 0.40 Hz (high frequency power). The average RR interval was also measured for each 5-minute segment.

Each 5-minute segment was categorized for its extent of ischemia as follows: (1) absent, if the segment contained no ST depression; (2) partial, if ST depression lasted less than the entire 5-minute segment; or (3) total, if ST depression was present throughout the entire 5-minute segment. Before statistical analysis, low and high frequency power values were subjected to logarithmic transformation to reduce the extreme skewness present in the original measurements. A mixed model 2-way analysis of variance for unequal sample sizes (the numbers of segments in the 3 categories varied both within and across patients) was carried out using program P3V of the BMDP package to make comparisons between the ischemic categories.⁵ Patients represented random effects and the 3 categories of ischemia (absent, partial or total) were analyzed as fixed effects.

The patient ages and characteristics of the ischemic episodes are listed in Table I. Nearly all the ischemic episodes (44 of 46) were asymptomatic. Many episodes were brief; the average duration was < 8 minutes. All but 1 episode of ST depression were associated with an increase in heart rate. On the average, the heart rate increased 15 beats/min during ischemic episodes. There was no significant difference in the mean heart rate between partial and total ischemic segments. Table II lists the mean values and their standard errors for RR interval, low frequency power, high frequency power and the ratio of low to high frequency power. Both the low frequency and high frequency power values decreased to about half their control values during segments with ischemic episodes. The ratio of low to high frequency power did not change significantly during segments with ischemia. The pattern of change clearly indicates a predominant decrease in parasympathetic activity without any detectable increase in sympathetic activity during ischemic episodes.

Our results indicate that withdrawal of parasympathetic neural activity accounts for the increase in heart rate during asymptomatic ST depression. Because parasympathetic modulation of RR intervals is distributed throughout the power spectrum range examined, a decrease in both the low and high frequency power bands is

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TABLE I Characteristics of Ischemic Episodes in Fifteen 24-Hour Ambulatory Electrocardiographic Recordings

Age (yrs)	64 ± 10*
No. of episodes per recording	2.9 ± 2.6
Maximum ST depression (mm)	1.7 ± 0.6
Duration of episodes of ST depression (min)	7.7 ± 13.0
Total ischemic time per recording (min)	22.5 ± 23.4

* Mean ± standard deviation.

reflected. The lack of an increase in the low frequency power or in the ratio of low frequency to high frequency power bands indicates that sympathetic activity did not increase significantly during ischemic segments. It should be noted that the average heart rate before an episode of ST segment depression was relatively slow, 80 ± 18 beats/min on the average, suggesting that there was a substantial amount of vagal tone and little if any sympathetic tone at the onset of the ischemic episodes. During ischemia, the average heart rate was 88 ± 19 beats/min, compatible with heart rate modulation by vagal withdrawal without sympathetic activation. Our results might not apply to more intense episodes of ischemia associated with marked ST segment depression, prolonged duration and pain. Such episodes might well cause activation of the sympathetic nervous system in addition to vagal withdrawal. Also, 5 patients were treated with β -blocking drugs, which may have reduced the influence of the sympathetic nervous system in the heart rate change during ischemic episodes.

There may be an analogy between the type of response seen in asymptomatic ST depression and that seen during mild exercise. The increase in heart rate during mild exercise is mediated predominantly by withdrawal of parasympathetic activity, while the still higher heart rate with more intense exercise is caused by vagal withdrawal plus an increase in sympathetic activity.^{6,7}

A decrease in parasympathetic tone has been shown to promote ventricular arrhythmias in experimental preparations.⁸ The dynamic withdrawal of vagal tone during periods of asymptomatic ST depression could contribute to the development of ischemic ventricular arrhythmias.

TABLE II Power Spectral Estimates of Autonomic Nervous Activity During Episodes of ST Depression in Fifteen 24-Hour Electrocardiographic Recordings

Measure	Ischemia Category for 5-Minute Periods		
	Absent (n = 4,044)	Partial (n = 67)	Total (n = 37)
Normal RR intervals (ms)	914 ± 39 [‡]	748 ± 43 [‡]	784 ± 52 [‡]
Low frequency power (ms ²)	586 ± 109	290 ± 153	200 ± 204
Ln low frequency power	2.38 ± 0.10	2.11 ± 0.12*	1.97 ± 0.15 [†]
High frequency power (ms ²)	193 ± 47	92 ± 70	118 ± 87
Ln high frequency power	1.89 ± 0.10	1.59 ± 0.11 [†]	1.53 ± 0.14 [†]
Ratio of low to high frequency power	4.60 ± 0.52	4.73 ± 0.73	4.10 ± 1.00
Ln ratio of low to high frequency power	0.49 ± 0.05	0.53 ± 0.07	0.45 ± 0.09

* Significantly different from the category with no ischemia at the p < 0.05 level;

† Significantly different from the category with no ischemia at the p < 0.01 level;

‡ mean ± standard error.

Ln = natural logarithm.

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Effects of Nifedipine SR and Enalapril on Office, Home and Ambulatory Blood Pressure in "White-Coat" Systemic Hypertension

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Among patients who were found to have hypertension by office or clinic blood pressure (BP) measurement, some appear to be normotensive when studied for full 24-

hour periods by ambulatory BP monitoring, indicating so-called "office" or "white-coat" hypertension. Within groups of hypertensive patients with similar office BPs, those with higher than predicted ambulatory BP have greater prevalence of target-organ damage^{1,2} and a significantly greater 10-year incidence of fatal and unfatal events than those with lower than predicted ambulatory BP.³ Moreover, there is some indication that reducing BP too much may exert a deleterious rather than a beneficial

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effect on coronary events.⁴ In the present study, we examined and compared the effects of the long-acting calcium antagonist nifedipine slow-release tablet (nifedipine SR) with the effects of the long-acting angiotensin converting enzyme inhibitor enalapril on office, home and ambulatory BP measurements. We studied hypertensive patients with relatively higher and relatively lower ambulatory BPs.

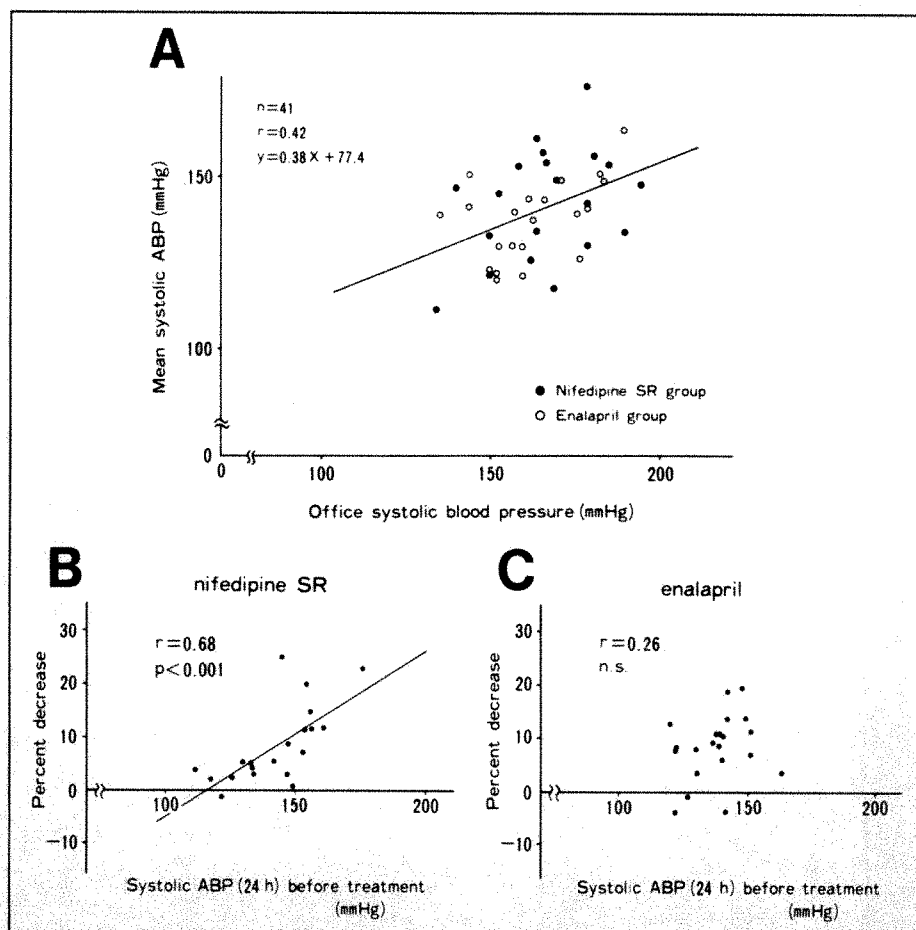
The study involved 41 Japanese outpatients, 19 men and 22 women, ranging in age from 25 to 67 years (average age \pm standard error of the mean, 54 ± 2). All patients had been diagnosed as having essential hypertension by excluding secondary forms of hypertension by standard clinical means. All patients were in World Health Organization hypertension stage I or II. Patients entered an 8-week control period during which no drug was given. At the end of this period, those patients whose seated systolic BP was ≥ 160 mm Hg, or whose seated diastolic BP was ≥ 90 mm Hg, or both, became eligible for the active treatment phase. They had 24-hour ambulatory BP monitoring and then entered an 8-week study phase, during which they randomly received either nifedipine SR or enalapril. In the nifedipine SR group (20 patients, mean age 54 ± 3), the dosage was 20 mg/day (10 mg twice daily) and in the enalapril group (21 patients, mean age 54 ± 2) the dosage was 5 or 10 mg/day (2.5 or 5 mg twice daily; final average dosage was 7.1 ± 0.6 mg/day). At the end of this 8-week phase, ambulatory BP monitoring was repeated in each patient.

At all 4-week interval visits during the study, office BP was measured by physicians using a standard mercury sphygmomanometer. Ambulatory BP was measured with automated portable monitors (ABPM 630, Nippon Colin Ltd.). This device uses a standard cuff that was placed around the upper arm and inflated at regular preset intervals (every 30 minutes in this study) throughout the entire day. Ambulatory BP was estimated by an oscillometric method. Each patient kept a record of activity undertaken during ambulatory BP monitoring. Sleeping ambulatory BP was calculated as the mean of ambulatory BP during sleep (by the patients' records). Waking ambulatory BP was calculated as the mean of waking ambulatory BP (by the patients' records).

Home BP was measured by patients with portable semiautomatic BP recorders twice a day, before morning and evening meals, in the seated position. All BP readings taken during 6 days at home (3 days before and after each hospital visit) were averaged and then recorded as the home BP.

There was a significant correlation between systolic office BP and systolic ambulatory BP in patients with essential hypertension ($r = 0.42$) (Figure 1A). Patients were classified into 2 groups according to the method previously described by Perloff et al³ with some modification. Patients whose observed systolic ambulatory BP was below the level predicted from the regression line between systolic ambulatory BP and systolic office BP were designated as the "low" ambulatory BP group

FIGURE 1. A, relation between office systolic blood pressure (BP) and mean systolic ambulatory BP (ABP) in patients with essential hypertension. Patients whose observed systolic ABP was below the level predicted from the regression line between systolic ABP and systolic office BP were designated as the "low" ABP group. Others were designated as the "high" ABP group. **B,C**, there was a significant correlation between mean systolic ABP before treatment and the percent decrease by nifedipine SR (**B**), but not by enalapril (**C**).



while others were designated as the "high" ambulatory BP group. Office BP was almost equal between the high group ($165 \pm 3/98 \pm 2$ mm Hg) and the low group ($164 \pm 3/98 \pm 2$ mm Hg). Ambulatory BP was $151 \pm 2/89 \pm 1$ mm Hg in the high group and $130 \pm 2/76 \pm 1$ mm Hg in the low group ($p < 0.001$). Figure 2 shows the percent decrease in systolic BP and diastolic BP for office, home and ambulatory (24 hours, waking and sleeping) BP during nifedipine SR or enalapril treatment in the high and low groups. Nifedipine SR tended to decrease office BP more than enalapril. In the high group, nifedipine SR tended to decrease ambulatory (24-hour) BP more than enalapril ($12.7 \pm 2.5/12.4 \pm 1.9$ vs $8.9 \pm 2/10 \pm 1.7\%$). In the low group, however, enalapril tended to decrease ambulatory (24-hour) BP more than nifedipine SR ($7.6 \pm 1.9/9.4 \pm 2.5$ vs $3.8 \pm 0.8/3.9 \pm 1.4\%$). Enalapril significantly decreased the sleeping ambulatory BP more than nifedipine SR ($7.9 \pm 2.0/9.7 \pm 2.3$ vs $3 \pm 1.5/$

$3.3 \pm 1.8\%$) ($p < 0.05$). When the high and low groups were compared, enalapril decreased ambulatory BP almost equally in the 2 groups, while nifedipine SR significantly decreased ambulatory BP in the high group more than it did in the low group ($p < 0.01$). Home BP was lower than office BP, but almost equal to ambulatory BP before treatment; however, during treatment with either drug, home BP did not decrease in parallel with ambulatory BP.

Mean systolic and diastolic ambulatory (24-hour) BP before treatment with nifedipine SR ($r = 0.68$ and 0.53 , respectively) correlated with the percent decrease (Figure 1B). Mean systolic and diastolic ambulatory BP before treatment with enalapril did not ($r = 0.26$ and 0.30 , respectively) (Figure 1C). Systolic office BP before treatment with either drug did not correlate with the percent decrease, but the correlation coefficient was larger with nifedipine SR ($r = 0.35$) than with enalapril ($r =$

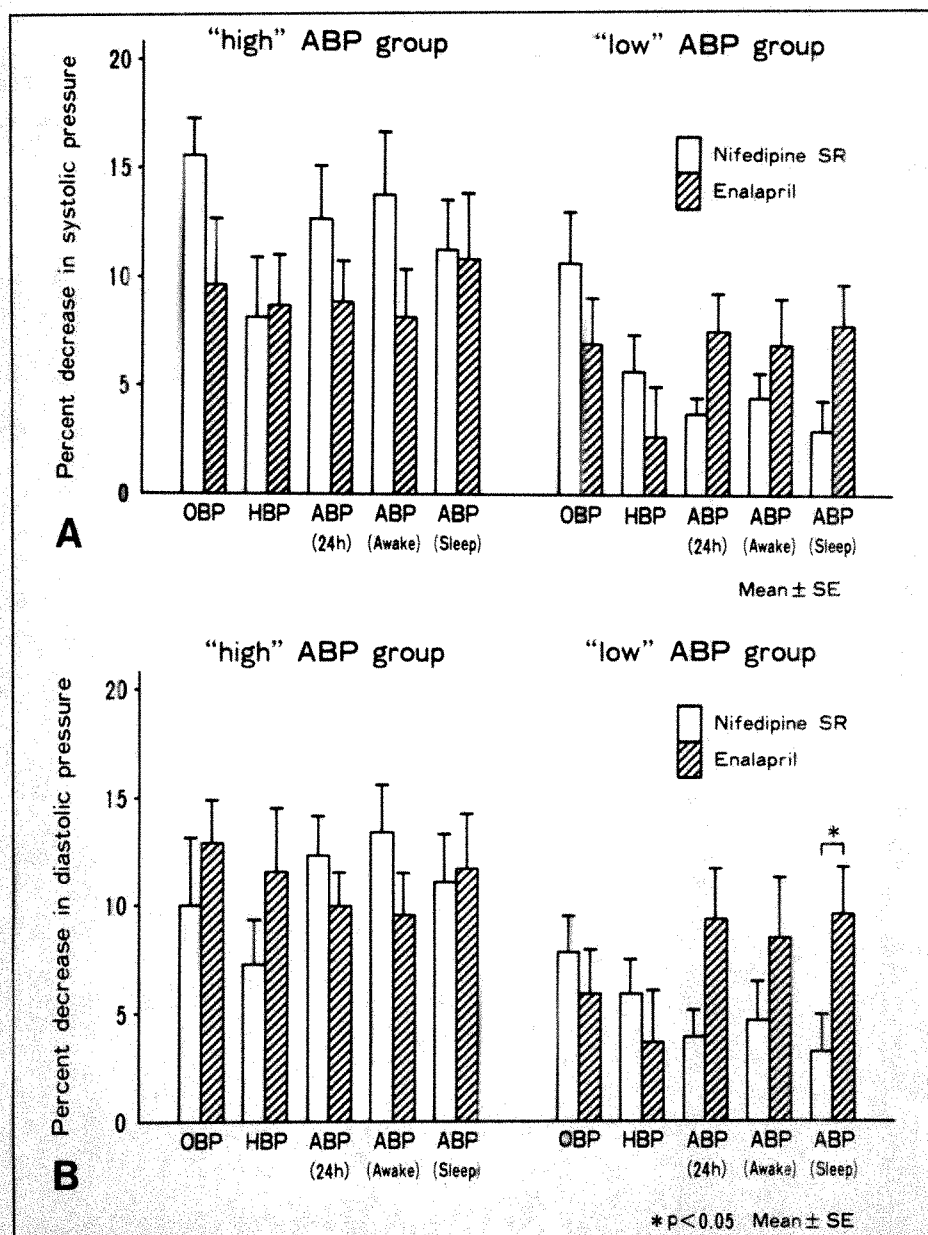


FIGURE 2. Percent decrease in systolic blood pressure (BP) (A) and diastolic BP (B) in office (OBP), home (HBP), and ambulatory (24 h, Awake, Sleep) BP (ABP) during treatment with nifedipine SR or enalapril in patients with higher than predicted ABP ("high" ABP group) and lower than predicted ABP ("low" ABP group).

0.18). There were no significant differences in 24-hour mean pulse rate between, before and during treatment with either nifedipine SR (69.6 ± 1.7 vs 70.6 ± 1.7 beats/min) or enalapril (71.4 ± 1 vs 70.7 ± 1.1 beats/min).

In this study, office and ambulatory BP measurements confirmed the efficacy of both nifedipine SR and enalapril therapy. Nifedipine SR tended to decrease office BP more than enalapril (Figure 2). There were, however, differences in ambulatory BP between the high and low groups. In the low group, enalapril decreased ambulatory BP more than nifedipine SR, while nifedipine SR decreased ambulatory BP in the high group more than enalapril. The higher the pretreatment ambulatory BP, the greater the ambulatory BP-lowering effect of nifedipine SR.

On the other hand, enalapril lowered the low pretreatment ambulatory BP to the same extent as it lowered the high pretreatment ambulatory BP. In other words, patients treated with nifedipine SR in the low group showed a small decrease in ambulatory BP measurements, but seemed to show a significant decrease in the office BP. In the low group, therefore, there was a clear difference between the effects nifedipine SR had on BP measured in the office compared to BP gauged by 24-hour ambulatory monitoring. The difference in measurements of BP with enalapril treatment was far smaller.

It may be an important property of nifedipine SR and other calcium antagonists^{5,6} that they do not decrease blood pressure in normotensive individuals. Weber et al⁵ recently reported that patients with "white-coat" hypertension derived almost no effect from diltiazem therapy on 24-hour BP analysis. They also reported that there was a correlation between baseline ambulatory BP and the diltiazem-induced antihypertensive effects. The relative weakness of hypotensive ambulatory BP responses in the low group of patients may be a desirable characteristic of calcium antagonists.

Increasing the dosage or the number of drugs in patients with "white-coat" hypertension may not always be harmless. There is a possibility of unnecessary increases in the number and severity of adverse effects. Moreover, lowering BP too much in some patients might be deleterious for blood flow to organs such as the coronary⁴ and cerebral⁷ vascular beds.

The present results are compatible with previous studies. MacGregor et al⁸ have reported that captopril lowered BP to the same extent in normotensive subjects as in hypertensive subjects. On the other hand, some investigators have reported that nifedipine had a greater effect on lowering higher initial BP.⁹⁻¹² Thus, converting enzyme inhibitors may exert their major action on BP through a mechanism that normally maintains BP, while nifedipine may reveal a functional abnormality of vascular smooth muscle that becomes greater the higher the BP.

In the present study, BP measured twice a day at home was almost equal to waking ambulatory BP before treatment. However, during antihypertensive treatment, home BP did not decrease in parallel with the mean waking ambulatory BP or with the mean sleeping ambulatory BP (Figure 2). This indicates that measuring BP twice a day at home may not be enough to predict the fluctuating BP levels during the day that occur in antihypertensive treatment. In this study we used enalapril twice a day to make a comparison with nifedipine SR. However, because enalapril can be given once a day, further studies should be done to compare the effects of enalapril administered once a day with a twice-daily dosage.

In summary, this study demonstrates that ambulatory BP may be valuable in identifying those hypertensive patients who are not hypertensive in daily life. Both nifedipine SR and enalapril decreased office BP significantly. However, the hypotensive effects on ambulatory BP measurements were different between the high and low groups. In the low group with "white-coat" hypertension, nifedipine SR decreased both waking and sleeping ambulatory BP less than enalapril did. These results suggest that there is a lesser chance of overtreating patients with "white-coat" hypertension with nifedipine SR than there is with enalapril.

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Echocardiographic Diagnosis of Unruptured Aneurysm of the Sinus of Valsalva Dissecting into the Ventricular Septum

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Congenital aneurysms of the sinus of Valsalva are uncommon and present mostly after their rupture.¹ Unruptured aneurysms of the sinus of Valsalva are rare and may present with arrhythmias, conduction abnormalities, right ventricular outflow obstruction, tricuspid regurgitation, aortic regurgitation or coronary conclusion.^{1,2} Their diagnosis during life is even rarer and most cases have been detected at autopsy or as incidental findings at angiography.² There are isolated case reports of echocardiographic diagnosis of such patients.²⁻⁴ We present herein 4 cases with echocardiographic diagnosis of this entity that were later confirmed by angiography and/or surgery.

Over the last 4 years, 35 cases of sinus of Valsalva aneurysms have been detected by cross-sectional and Doppler echocardiography in our center. This report pertains to 4 unruptured aneurysms originating from the right sinus of Valsalva and dissecting into the ventricular septum. In the 31 cases of ruptured aneurysms, the right sinus was involved in 29 (rupture into right ventricle in 28 and into left ventricle in 1) and the noncoronary sinus in 2 (rupture into right atrium in both). There was no echocardiographic or clinical evidence of endocarditis in any of the 4 unruptured patients, although vegetations were detected in 5 of the 31 patients with ruptured aneurysms. All 4 patients with unruptured aneurysms were men with an age range of 20 to 45 years. Three of these patients presented with syncope caused by complete heart block. Other manifestations included progressive dyspnea (in 3 patients), moderate aortic regurgitation (in 3 patients) and mitral regurgitation (in 1 patient).

On 2-dimensional echocardiography, all 4 patients showed the aneurysm as a cystic mass in the upper part of the ventricular septum clearly communicating with the right coronary sinus of Valsalva (Figure 1). The wall of the aneurysm showed dense echoes suggestive of calcification in 3 patients. This was confirmed on cinefluoroscopy. The fourth patient had a huge noncalcific aneurysm (8 cm × 5 cm × 3 cm in size) that projected into the left ventricular cavity and showed diastolic expansion and systolic collapse (Figure 2). Aneurysms with calcified walls did not change appreciably in size with the cardiac cycle. In the last 3 patients, pulsed-Doppler interrogation at the site of the communication of the aneurysm with the aorta showed a to and fro signal (Figure 2). Additional Doppler echocardiographic findings included moderate aortic regurgitation in 3 patients, mild mitral regurgitation in 1 (patient 2) and innominate artery block in 1 (patient 3); all were confirmed by angiog-

raphy. Etiology of the innominate artery block is not clear. Left ventricular function was depressed (left ventricular ejection fraction 0.3, 0.4 and 0.45) in 3 patients (all with calcified walls). All 4 patients were subjected to cardiac catheterization and angiography that confirmed the findings obtained by 2-dimensional and Doppler echocardiography. Two patients (1 and 2) were operated upon. The surgery involved closure of the aortic end of the aneurysm in both and aortic valve replacement in 1. The echocardiographic findings were confirmed at surgery. Permanent pacemaker implantation was required in the 3 patients presenting with syncope. All the patients are doing well on follow-up.

Unruptured aneurysms of the sinus of Valsalva may dissect into the upper part of the ventricular septum, causing conduction abnormalities and aortic regurgitation.²⁻⁵ There are 3 previous reports of unruptured aneu-

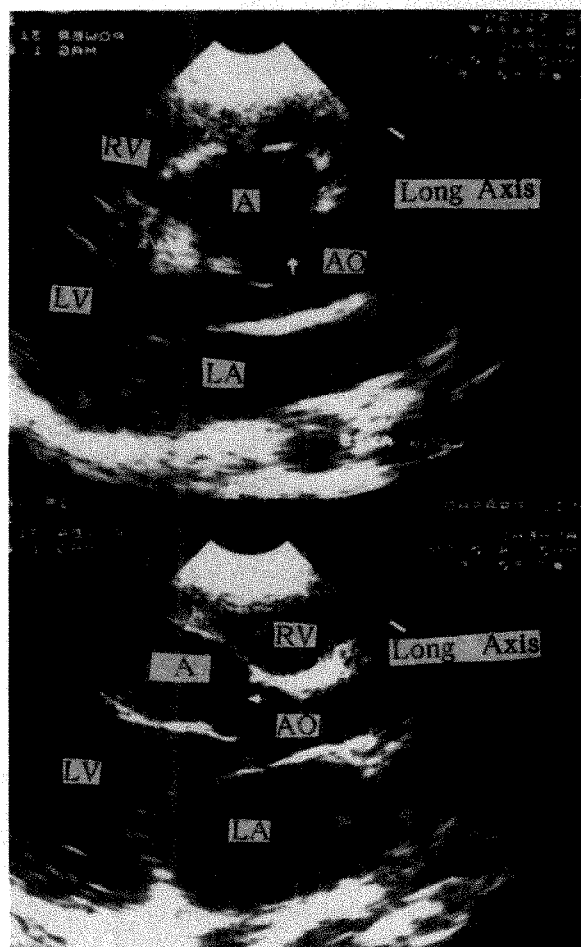


FIGURE 1. Two-dimensional echocardiography. Long-axis views of the 2 patients showing sinus of Valsalva aneurysms (A) dissecting into the upper part of interventricular septum. AO = aorta; RV = right ventricular; LV = left ventricular.

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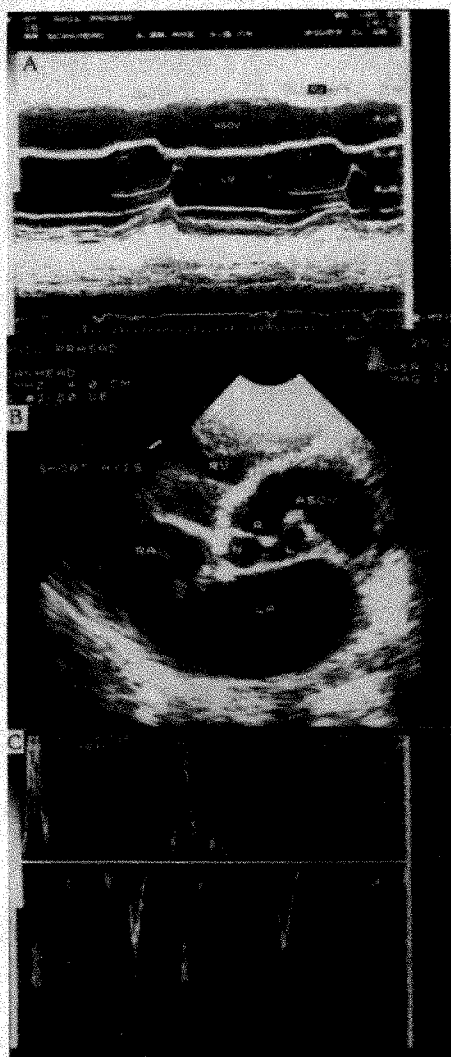


FIGURE 2. A, M-mode cut at the level of mitral valve showing systolic collapse and the diastolic expansion of the aneurysm in the interventricular septum. B, short-axis view at the level of aortic valve clearly showing communication of the aneurysm with right coronary sinus (R). C, to and fro Doppler signal at site of the communication of aneurysm with right coronary sinus. ASOV = aneurysm of the sinus of Valsalva; L = left coronary sinus; LA = left atrium; N = noncoronary sinus; RA = right atrium; RV = right ventricle.

rysms dissecting into the ventricular septum, diagnosed on echocardiography.³⁻⁵ The aneurysms present like a "cyst" in the upper part of the ventricular septum. The diagnosis is based upon demonstration of the communication of the aneurysm with the sinus of Valsalva.³⁻⁵ This was demonstrable in all our patients. Enlargement of the aneurysm during diastole and collapse during systole has been found to be a useful finding.³⁻⁴ We found this to be useful in only 1 of our patients. Calcification of the aneurysm wall possibly prevents change in its size with cardiac contraction. A to and fro Doppler signal at the mouth of the aneurysm was present in 3 of our patients in whom it was specifically looked for. We believe the echocardiographic diagnosis of this entity should be based upon the demonstration of a cystic space in the ventricular septum communicating with a sinus of Valsalva, and a to and fro Doppler signal at the site of communication.

Conduction abnormalities occurred in all our patients (complete heart block in 3 and bifascicular block in 1) and are caused by disruption of the conduction tissue by the dissecting aneurysm. Aortic regurgitation was present in 3 cases and was related largely to the distortion of the aortic valve by the aneurysm, as the valve leaflets appeared anatomically normal. The cause of poor left ventricular function in these patients is unclear. Mechanical interference with the septal motion because of the aneurysm, aortic regurgitation and extension of the calcification into the myocardium may be contributory. Combined cross-sectional and Doppler echocardiography is valuable in the diagnosis of this entity.

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Coenzyme Q₁₀ and Respiratory Chain Enzyme Activities in Hypertrophied Human Left Ventricles with Aortic Valve Stenosis

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Morphologic studies on left ventricular myocardium of patients with aortic stenosis revealed increased muscle fiber diameter and increased interstitial fibrosis compared to control subjects.¹ Biochemical studies showed that in patients with aortic stenosis, the subendocardial levels of high-energy phosphates were decreased compared to nonhypertrophied myocardium.² It was suggested that in these patients, the decreased adenosine triphosphate stores contribute to the enhanced sensitivity of the heart to ischemia. Coenzyme Q₁₀ is a central and rate-limiting compound of the mitochondrial respiratory chain, which generates most of the adenosine triphosphate in the cell. It has been shown that oral administration of coenzyme Q₁₀ was an effective therapy not only in patients with cardiomyopathy,³ but also in various other cardiovascular diseases.⁴ This study shows that left ventricular coenzyme Q₁₀ concentrations increase with the degree of aortic stenosis, resulting in increased activities of the coenzyme Q₁₀-dependent respiratory chain enzyme reactions.

Myocardial biopsies were obtained during open-heart surgery from the apex of the left ventricle from 8 patients with pure aortic stenosis who underwent surgery for aortic valve replacement. According to the guidelines of the New York Heart Association, 1 patient was in class I, 4 in class II and 3 in class III. Specimens were immediately frozen and stored in liquid nitrogen. The aortic valve pressure gradient between the left ventricle and aorta was measured by left-sided heart catheterization.

The activities of the respiratory chain enzymes were measured in homogenates of the muscle biopsies. Activities of total NADH cytochrome-c-oxidoreductase, antimycin A-sensitive NADH cytochrome-c-oxidoreductase (complexes I + III), succinate dehydrogenase, succinate cytochrome-c-oxidoreductase (complexes II + III), cytochrome-c-oxidase (complex IV) and of citrate synthase were determined spectrophotometrically.⁵ Coenzyme Q₁₀ was measured in muscle homogenates and in serum obtained immediately before the initiation of anesthesia using a high-pressure liquid chromatography method.⁶ Noncollagen protein was assayed after digestion of the homogenate with sodium hydroxide (50 mmol/liter) and pelleting the insoluble collagen protein by centrifugation (12,000 g for 10 minutes).

A positive correlation ($p < 0.05$) of the coenzyme Q₁₀ concentration with the aortic valve pressure gradient was found, both whether coenzyme Q₁₀ concentration was

expressed per noncollagen protein ($r = 0.77$) (Figure 1) or per muscle wet weight ($r = 0.81$). The coenzyme Q₁₀-dependent activities of the respiratory chain complexes I + III were 1.8-fold higher and those of complexes II + III were 1.5-fold higher in ventricles with aortic valve pressure gradients of 60 to 90 mm Hg than in those with pressure gradients of 50 to 60 mm Hg. However, activities of cytochrome-c-oxidase and of citrate synthase, a mitochondrial matrix enzyme, as well as noncollagen protein content remained unchanged. There was neither a significant correlation between the myocardial coenzyme Q₁₀ concentration and the patients' functional class nor between myocardial and serum coenzyme Q₁₀ levels.

Our data indicate that in left ventricular hypertrophy due to aortic stenosis, the capacity of the mitochondrial respiratory chain increases with increasing hemodynamic stress. Because only the coenzyme Q₁₀-dependent enzyme activities (complexes I + III and II + III), but not the coenzyme Q₁₀-independent activities (complex IV and citrate synthase) increased, it was most likely the

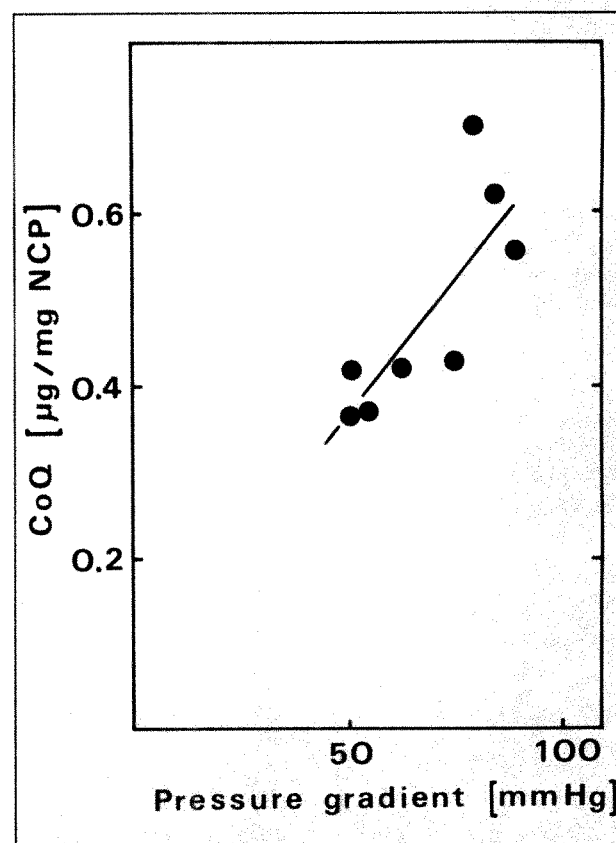


FIGURE 1. Coenzyme Q₁₀ concentrations in left ventricle of patients with aortic stenosis with different aortic valve pressure gradients. Correlation coefficient was 0.77 ($p < 0.05$). CoQ = coenzyme Q₁₀; NCP = noncollagen protein.

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increased coenzyme Q₁₀ concentration that primarily caused the biochemical changes. Therefore, the changes of myocardial coenzyme Q₁₀ concentrations might represent a metabolic response to the increased myocardial energy demand in aortic stenosis. Because the subendocardial levels of high-energy phosphates were decreased in hypertrophied left ventricle compared to nonhypertrophied myocardium,² it is possible that the "physiologic" accumulation of coenzyme Q₁₀ does not sufficiently compensate for the increased energy demand of the hypertrophied myocardium. Thus, exogenous administration of coenzyme Q₁₀ might be beneficial in patients with aortic stenosis by correcting a functional coenzyme Q₁₀ deficiency state.

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The Probability of Detecting a Subaortic Ridge in Children with Ventricular Septal Defect or Coarctation of the Aorta

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Membranous subaortic stenosis can be found as an isolated congenital defect or in association with other congenital heart lesions such as ventricular septal defect (VSD)¹⁻⁷ or coarctation of the aorta (C of A).⁸ Recent reports have suggested an increased incidence of membranous subaortic stenosis in patients with VSD and right ventricular muscle bundles,⁹ malalignment VSD¹⁰ and ventricular septal aneurysm.¹¹⁻¹⁴ Membranous subaortic stenosis develops and progresses over time¹⁵⁻¹⁷ and usually requires surgery. Subaortic stenosis is often associated with damage and thickening of the aortic valve, leading to aortic valve regurgitation.¹⁸⁻²⁰ In patients with VSD, ventricular septal aneurysm or C of A, we have observed an echogenic ridge of tissue in the left ventricular outflow tract that may be a precursor to membranous subaortic stenosis. To determine the probability of detecting a subaortic ridge in patients with VSD in different locations and in patients with C of A, and to determine if ventricular septal aneurysm increases the probability of detecting a subaortic ridge in patients with perimembranous VSD, we reviewed the echocardiographic records of our patients with VSD, subaortic ridge or C of A.

Our database consisted of 7,763 patients examined in our pediatric echocardiography laboratory between January 1980 and August 1988. The study population was confined to 1,061 patients with echocardiographic diagnoses of perimembranous VSD, ventricular septal aneurysm, muscular VSD, doubly committed subarterial VSD or C of A. The study population was comprised of 602 male and 493 female patients. Their mean age was 4.4 (± 6.1 [standard deviation]), median age 1.7 and

maximum age 55 years. Patients with other significant heart diseases were excluded.

The following definitions were used. Subaortic ridge, called fixed subaortic abnormality,⁹ fixed subaortic stenosis,¹⁷ subaortic fibrous ridge¹⁰ or discrete subaortic stenosis,¹² was defined as a ridge-like protrusion into the subaortic area from the crest of the ventricular septum that extended toward or inserted into the mitral valve apparatus (Figure 1). This ridge was seen in the parasternal long-axis and apical 2- and 4-chamber views. This definition did not require Doppler evidence of tur-

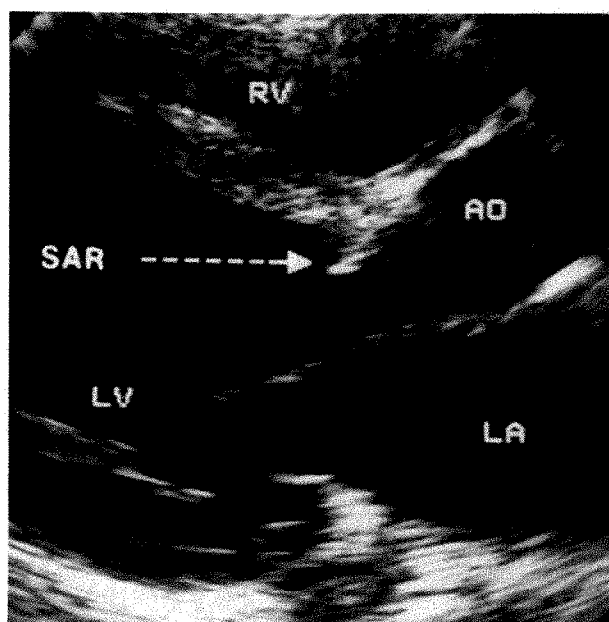


FIGURE 1. Echocardiographic finding of a subaortic ridge in the parasternal long axis view. The subaortic ridge (SAR) is indicated by the arrow. AO = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle.

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TABLE I Number of Patients with Subaortic Ridge with Each Possible Associated Factor

Diagnosis	With SAR	Without SAR	Total	% With SAR
Subaortic ridge only	34	0	34	100.0
Study Population				
Perimembranous VSD, VSA + C of A	4	11	15	26.7
Perimembranous VSD + C of A	5	16	21	23.8
Muscular VSD + C of A	2	8	10	20.0
Doubly committed subarterial VSD only	5	48	53	9.4
C of A only	20	199	219	9.1
Perimembranous VSD only	16	207	223	7.2
Perimembranous VSD + VSA	20	350	370	5.4
VSA only	2	46	48	4.2
Doubly committed VSD + C of A	0	2	2	0.0
Muscular VSD only	0	84	84	0.0
VSA + C of A	0	3	3	0.0
Miscellaneous combinations	0	13	13	0.0
Total in study population	74	987	1061	7.0
Total pts studied in interval	108	7655	7763	1.4

C of A = coarctation of the aorta; SAR = subaortic ridge; VSA = ventricular septal aneurysm; VSD = ventricular septal defect.

bulent flow or obstruction. Ventricular septal aneurysm²¹ was defined as the accessory tricuspid tissue often found in patients with perimembranous VSD. This aneurysm-like tissue is most often found on the right ventricular side of the VSD, partially closing the defect.

All reports and diagnoses from patients in the database were reviewed. The presence of VSD, ventricular septal aneurysm, subaortic ridge or C of A was determined by the echocardiographic description of the anatomy or echocardiographic diagnosis. Thirty-four patients with subaortic ridges or membranous subaortic stenosis without VSD, ventricular septal aneurysm or C of A were excluded; 19 of these patients had serial echocardiograms and were considered when evaluating the progression of the subaortic ridge.

TABLE II Hazard Coefficients for the Different Possible Associated Factors Alone and in Combination When Compared to Patients with Isolated Perimembranous VSD

Associated Factor(s)	Hazard Coefficient	Standard Error	p Value
Perimembranous VSD + C of A	1.473	0.3751	0.0001
Muscular VSD + C of A	2.0913	0.7336	0.0044
Doubly committed subarterial VSD	-0.4050	0.4809	0.3997
Muscular VSD	-7.630	26.82	0.7760
C of A	0.0597	0.2825	0.8327
Muscular + doubly committed subarterial VSDs	-7.593	94.71	0.9361
Perimembranous + muscular VSDs + C of A	-7.696	317.7	0.9807
Perimembranous + muscular VSDs	-7.639	98.66	0.9383
Doubly committed subarterial VSD + C of A	-7.704	242.5	0.9747

Abbreviations as in Table I.

Five different possible associated factors were identified: perimembranous VSD, muscular VSD, doubly committed subarterial VSD, ventricular septal aneurysm or C of A. A Cox proportional hazards model was used to estimate the effects of these factors on the time until detection of the subaortic ridge. This analysis was performed on a computer using the SAS statistics program. Chi-square with Yates's correction was used to examine the association between ventricular septal aneurysm and subaortic ridge. A p value of ≤ 0.05 was considered significant.

Serial echocardiographic examinations were performed in 44 patients with subaortic ridge or subaortic stenosis during the study interval. These studies were reviewed to ascertain the progression of the subaortic ridge in this limited subpopulation.

Of the 1,061 patients in the study population, 636 (60%) had perimembranous VSD, of whom 388 (37%) also had a ventricular septal aneurysm, 48 (4.5%) had ventricular septal aneurysm and no VSD, 102 (9.6%) had muscular VSD, 61 (5.7%) had doubly committed subarterial VSD and 199 (19%) had isolated C of A

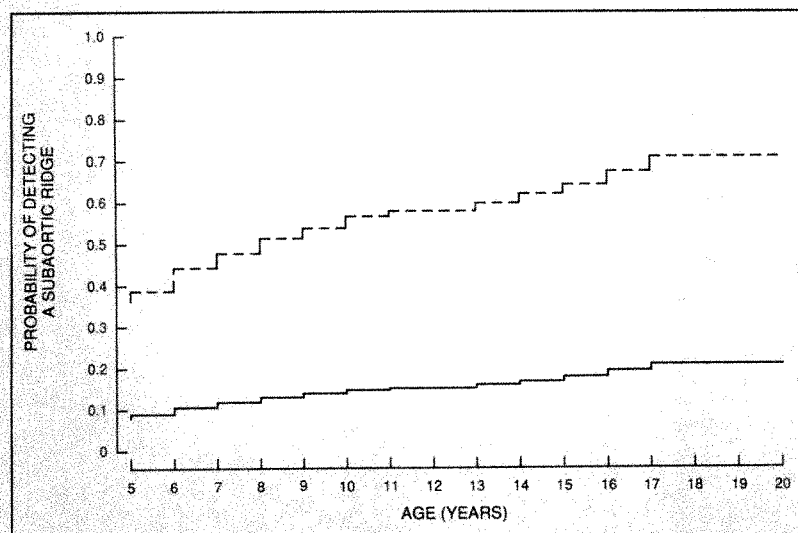
**FIGURE 2.** Probability curve demonstrating the effect of coexisting coarctation of the aorta and of either perimembranous or muscular ventricular septal defect on the probability of detecting a subaortic ridge. The solid line represents the probability of detecting a subaortic ridge for patients with isolated perimembranous ventricular septal defect, who represent all patients with any single factor. The broken line represents the probability of detecting a subaortic ridge for patients with coarctation of the aorta and either perimembranous or muscular ventricular septal defect.

TABLE III Findings from Serial Studies in Patients with a Subaortic Ridge

Echocardiographic Finding	No. of VSD Pts	No. of Non-VSD Pts	Mean Age at Last Examination (yrs \pm SD)	Mean Duration of Follow-up (yrs \pm SD)
Subaortic ridge detected	13	1	4.8 \pm 4.1	3.4 \pm 2.1
Increased obstruction	4	7	6.9 \pm 4.8	2.6 \pm 1.8
Developed aortic insufficiency	1	2	7.4 \pm 1.1	4.2 \pm 1.0
No interval change	7	9	8.8 \pm 6.0	3.7 \pm 3.2
Improved	0	0		
Total	25	19	6.9 \pm 5.1	3.4 \pm 2.4

SD = standard deviation; VSD is ventricular septal defect.

(Table I). C of A was found in 50 of 741 (6.8%) of patients with VSD, including 36 of 629 (5.7%) with perimembranous, 10 of 94 (10.6%) with muscular, 2 of 60 (3.3%) with doubly committed subarterial and 2 of 6 with multiple VSDs. A subaortic ridge was found in 74 (7.0%) patients in the study population, including 45 (7.2%) with perimembranous VSD, 26 (5.9%) with ventricular septal aneurysm, 2 (2.1%) with muscular VSD, 5 (8.3%) with doubly committed subarterial VSD and 31 (11.4%) with C of A.

A subaortic ridge was found more frequently in the study population than in the 7,763 patients in the database ($p < 0.001$). The Cox proportional hazards model demonstrated that in the sample of patients having at least 1 of the identified factors, only C of A and either perimembranous or muscular VSD accelerated the time until detection of the subaortic ridge (Table II). No single factor increased the probability of detection over that of isolated perimembranous VSD. The presence of a ventricular septal aneurysm did not increase the probability of detection of subaortic ridges over that of patients with isolated perimembranous VSD. No single condition was statistically different from isolated perimembranous VSD, as indicated by the large p values. In addition, the age of patients with perimembranous VSD alone (4.4 ± 5.3 , mean \pm standard deviation) and the median age of this subgroup (1.7 years) were not different from the study population. This suggests that the study population could be represented by patients with isolated perimembranous VSD.

Figure 2 shows how the failure curve (1 - survival) is affected by having C of A and either a perimembranous or a muscular VSD in comparison to all cases with isolated VSD or C of A alone. The Cox proportional hazards analysis predicts that the probability of detecting a subaortic ridge increases for all patients in the study population as their age increases. There was a 20% predicted probability of detecting a subaortic ridge in the study population by age 18, and a 60% predicted probability among patients with both C of A and perimembranous or muscular VSD.

During the study interval, 44 patients with a subaortic ridge had 2 or more serial studies. These findings are listed in Table III. The development of a recognizable subaortic ridge or increased left ventricular outflow obstruction was observed in 17 of 25 patients with VSD and in 8 of 19 patients with a subaortic ridge alone. In addition, only 1 of 25 patients with VSD and 2 of 19 patients

with a subaortic ridge alone developed evidence of aortic valve regurgitation. Sixteen of the 44 patients (7 with and 9 without VSD) showed no interval change over an average of 3.7 years of follow-up.

This study shows that a subaortic ridge is more commonly found among patients with VSD or C of A than in patients in the database and that the relative probability of detecting a subaortic ridge is higher in patients who have both VSD and C of A. Furthermore, ventricular septal aneurysm is not an associated factor independent of perimembranous VSD. Longitudinal observation in a limited subpopulation supports the contention that this is a progressive lesion in some patients.

The predicted probability of detecting a subaortic ridge is higher over time than previously thought. This is perhaps due to the fairly high rate of appearance of a subaortic ridge in many very young patients. Although the Cox proportional hazards model allows calculation of the probability of detection of a subaortic ridge for any patient given their risk factors, it has a limited ability to evaluate a patient's natural history. In addition, many of the patients included in the study group have had surgery, which may have influenced the development of a subaortic ridge or unmasked it in some patients.¹²

The definition of what constitutes subaortic stenosis is important to appreciate because of the exquisite ability of echocardiography to recognize small fibrous ridges. Previous studies define even small subaortic ridges as subaortic stenosis.^{9,10} Many investigators argue that the presence of a ridge requires surgical intervention when attacking an associated lesion.^{9,10} The progressive nature of subaortic stenosis (even after surgical resection) has been established^{15,16} and is supported by the progression of obstruction seen in the limited number of patients followed serially in this study.

All patients with a membrane-like echodense protrusion into the left ventricular outflow were considered to have a subaortic ridge. Before the wide use of echocardiography, many of these protrusions were undetectable and only infrequently developed into clinically significant obstructions. We consider this protrusion to be part of the spectrum of subaortic stenosis. There are, however, no data to suggest that all of the lesions that are detected echocardiographically will become hemodynamically important, as has been suggested by others^{9,17} and a dilemma exists as to whether resection of these lesions is required.

This study shows that the highest probability of de-

tecting subaortic ridges is in patients who have both C of A and either perimembranous or muscular VSD. The probability of detecting a subaortic ridge increases with time and warrants serial examinations. Because this subaortic ridge may be a precursor to membranous subaortic stenosis, these patients need close clinical follow-up and serial echocardiograms.

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Left Ventricular Pseudohypertrophy in Pericardial Effusion as a Sign of Cardiac Tamponade

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There is probably not one single pathologic condition that has been studied by echocardiography as extensively as pericardial effusion and cardiac tamponade. Among the many reported echocardiographic signs of cardiac tamponade, the most frequent and diagnostically useful are the following: right ventricular and right atrial diastolic collapse^{1,2}; a "swinging heart"³; and phasic respiratory changes of ventricular dimensions.⁴ This report describes a new echocardiographic sign, typical for pericardial effusion and tamponade, namely a transient thickening of left ventricular (LV) wall associated with cardiac tamponade.

Among 82 consecutive echocardiographic examinations (76 retrospective and 6 prospective) performed because of a large pericardial effusion and/or cardiac tamponade, 16 cases with signs of LV hypertrophy were found. Nine cases with LV hypertrophy in the echocardiogram with pericardial effusion and in that recorded after removal of the pericardial fluid were classified as true LV hypertrophy and thus not included for further analyses. Seven cases with thickened LV wall during

cardiac tamponade and normal LV wall thickness at the control echocardiogram were classified as LV pseudohypertrophy and represented the study group. Each of the 7 cases had cardiac tamponade diagnosed by clinical signs and echocardiographic findings. In all patients, heart rate decreased by ≥ 10 beats/min and hypotension and neck vein distension disappeared after removal of pericardial fluid. In 2 patients prospectively studied, cardiac output and right-sided, brachial and pericardial pressures were measured. Echocardiograms were performed either with an Aloka 720 mechanical sector scanner or an Aloka 870 phased-array echocardiographic system. Two-dimensional and M-mode echocardiograms were obtained in each patient. An echo-

TABLE I Left Ventricular Pseudohypertrophy Clinical Data

Patient	Sex	Age	Pericardial Fluid	Etiology
1	F	16	Serous	SLE
2	M	40	Blood	Trauma
3	M	82	Serosanguineous	Viral
4	M	75	Serosanguineous	TB
5	F	19	Serous	SLE
6	F	72	Serosanguineous	Idiopathic
7	F	40	Serous	Lymphoma

SLE = systemic lupus erythematosus; TB = tuberculosis.

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TABLE II Left Ventricular Pseudohypertrophy Echocardiographic Data

Patient	SEPD (mm)		SEPS (mm)		PWD (mm)		PWS (mm)		LVED (mm)		LVS (mm)		LV Length (mm)		M-Mode LV Mass (g)		2-D LV Mass (g)		PE (mm)
	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	
1	17	11	22	15	17	8	19	14	38	42	29	30	54	62	265	128	226	165	14
2	17	9	21	12	17	8	21	13	38	46	—	27	—	—	265	127	—	—	15
3	16	11	16	14	10	10	15	13	45	50	36	35	—	—	223	194	—	—	25
4	15	9	20	11	10	9	19	13	40	46	29	31	—	—	176	141	—	—	20
5	20	11	20	16	19	10	22	18	48	50	31	26	57	78	456	194	290	138	18
6	17	12	20	19	17	12	26	19	35	45	19	32	54	66	238	198	274	174	44
7	13	8	14	10	19	10	21	13	32	40	13	23	68	72	185	109	181	92	34
Mean	16	10	19	14	15	9	20	15	39	45	26	29	58	69	258	155	242	142	
SD	2	1	3	3	4	1	3	2	5	3	8	4	6	7	93	38	49	36	
p value																			
T vs C	<0.0001		<0.005		<0.007		<0.0001		<0.001		NS		<0.05		<0.01*		<0.01		

* Difference not significant vs 2-dimensional (2D) left ventricular (LV) mass. C = echocardiographic measurements after removal of pericardial fluid; LVED = left ventricular end diastolic dimension; LVS = left ventricular systolic dimension; NS = not significant; PE = width of posterior pericardial space during tamponade; PWD = posterior-wall diastolic thickness; PWS = posterior-wall systolic thickness; SEPD = interventricular septal diastolic thickness; SEPS = interventricular septal systolic thickness; T = echocardiographic measurements during cardiac tamponade; 2D = 2-dimensional.

cardiogram was recorded in each case during cardiac tamponade; the control echocardiogram was recorded immediately after the pericardiocentesis in 5 cases and 5 and 30 months later in 2 cases. Echocardiographic measurements were performed according to the recommendation of the American Society of Echocardiography.⁵ LV mass was calculated from M-mode tracing using the

following formula⁶: $0.80 \times (1.04 [LVED + VS + LVPW]^3 - [LVED]^3) + 0.6$ g, where LVED = LV end-diastolic dimension, VS = diastolic thickness of the ventricular septum and LVPW = diastolic thickness of the posterior wall. In 4 patients with adequate recording of short-axis and apical 4-chamber views in both tamponade and control studies, LV mass was calculated from 2-

FIGURE 1. Two-dimensional echocardiogram in the long-axis view (left) and relative M-mode tracing during cardiac tamponade (right, case number 1). Left ventricle is severely thickened. Ventricular septal and posterior wall diastolic thickness are 17 mm each. A moderate pericardial effusion is seen. The echocardiographic myocardial texture is characterized by highly reflective echoes. Distance between dots is 10 mm.

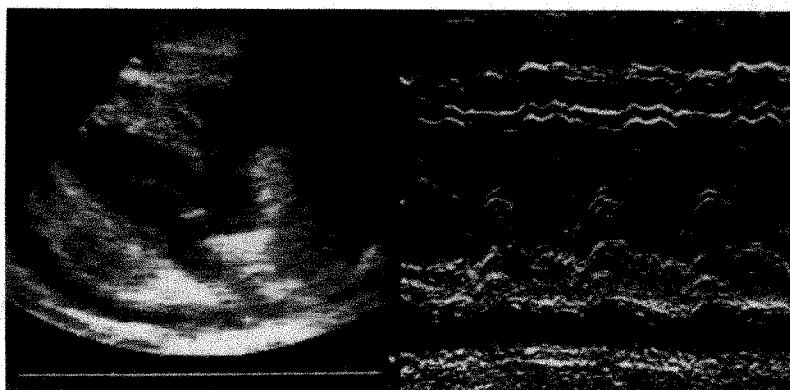
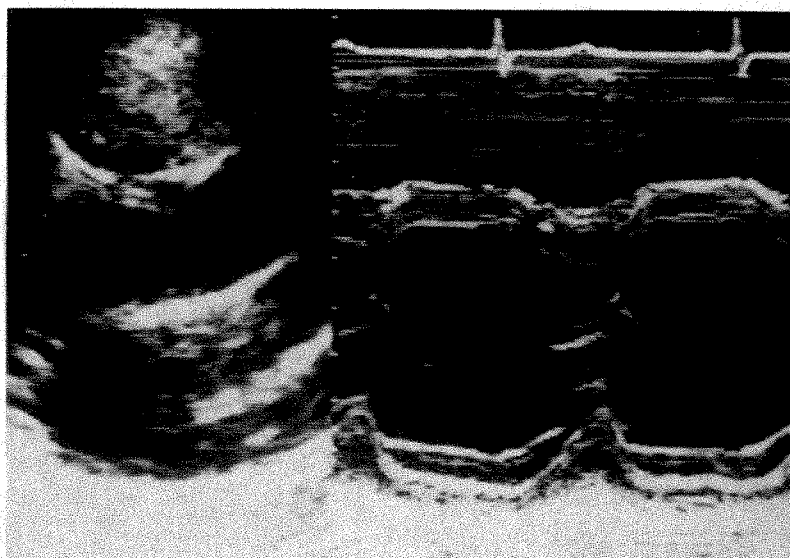


FIGURE 2. Two-dimensional (left) and M-mode echocardiogram (right) of case number 1 taken immediately after aspiration of pericardial fluid. The pericardial effusion disappeared. Wall thickness returned to normal (ventricular septal diastolic thickness 10 mm and posterior wall thickness 8 mm). Distance between dots is 10 mm.



dimensional echocardiogram according to the following formula⁷: $1.055 \times 5/6 (A_1 L_1 - A_c L_c)$, where A_1 = end-diastolic short-axis LV area at the high papillary muscle level including the edges of the outer LV myocardial boundaries, L_1 = LV cavity length measured from the apex to the midmitral annulus plane with 1 cm added, A_c = LV cavity area and L_c = LV cavity length. Myocardial reflectivity was subjectively assessed and defined either as normal or increased when highly reflective echoes were detected.⁸

Statistical analysis was performed by using a paired Student's *t* test.

Clinical data are listed in Table I. Cardiac rhythm was sinus in 5 patients and atrial fibrillation in 2. Additional cardiovascular diseases included mild systemic hypertension in 3 patients and old diaphragmatic myocardial infarction in 2. Two patients were on hemodialysis the week before the development of tamponade. Hemodynamic measurements were done in patient numbers 6 and 7. In the first patient during tamponade, mean pericardial pressure was 17 mm Hg, brachial artery pressure 115/70 mm Hg, mean right atrial pressure 12 mm Hg, pulmonary artery pressure 35/20 mm Hg and cardiac output 3.3 liters/min. After aspiration of 900 ml of fluid, pericardial pressure decreased to 0, brachial artery pressure increased to 160/65 mm Hg, mean right atrial pressure was 10 mm Hg, pulmonary pressure 77/25 mm Hg and cardiac output 4.8 liters/min. In the second patient during cardiac tamponade, mean pericardial pressure was 14 mm Hg, mean right atrial pressure 12 mm Hg, pulmonary artery pressure 30/12 mm Hg, aortic pressure 90/54 mm Hg and cardiac output 3.9 liters/min. After removal of 580 ml of fluid, pericardial pressure decreased to 4 mm Hg, mean right atrial pressure was 8 mm Hg, pulmonary artery pressure 28/8 mm Hg, aortic pressure 100/55 mm Hg and cardiac output 5.3 liters/min.

The unique observation in these patients was the marked thickening of left ventricular wall (Table II and Figures 1 and 2). The mean diastolic ventricular septal thickness was 16 ± 2 mm and the posterior wall thickness was 15 ± 4 mm. After aspiration of the fluid, the mean diastolic ventricular septal thickness was decreased to 10 ± 1 mm ($p < 0.0001$) and the mean diastolic posterior wall thickness to 9 ± 1 mm ($p = 0.007$). Similar changes of the systolic dimensions were also observed. In 2 patients (numbers 3 and 4) with old diaphragmatic myocardial infarction, only the ventricular septum thickened during cardiac tamponade.

The calculated LV mass was increased during cardiac tamponade. M-mode echocardiography-calculated mean LV mass was 258 ± 93 g. After aspiration, LV mass returned to normal values (< 250 g) in each case with an average value of 155 ± 38 g ($p < 0.01$). Mean LV mass from 2-dimensional echocardiography was 242 ± 49 g during cardiac tamponade and 142 ± 36 g after aspiration ($p < 0.01$). No statistically significant difference was found between M-mode and 2-dimensional-calculated LV mass values.

Right atrial and right ventricular diastolic collapse

were present in 4 cases, a "swinging heart" was present in 2 cases and phasic respiratory changes of the ventricular dimensions were present in 2 of the 5 patients who were in sinus rhythm.

An increased reflectivity of the LV walls was observed in 4 cases during cardiac tamponade, but not after aspiration of the pericardial fluid (Figure 1).

Two features are striking in the patients presented in this study. The appearance of LV wall thickening was closely associated with pericardial effusion and tamponade. It was absent in 2 cases before tamponade and disappeared in all patients after the removal of the pericardial fluid. The second important point is the increase in calculated LV mass. This is a crucial measurement as it indicates a true increase in the size of the LV walls. A simple decrease in LV diastolic and systolic diameters, as it occurs in tamponade, would be obviously associated with some degree of wall thickening. However, the significant and marked increase in LV mass precludes any possibility that the decrease in LV dimensions are the sole basis for the wall thickness changes. The increase in LV mass was observed also when this parameter was measured from 2-dimensional echocardiographic recording even though a change in the LV shape was also noticed; the LV long axis decreased proportionally more than the short axis, giving the ventricle a rounded appearance.

This possibly true increase in LV mass may be explained by myocardial congestion and interstitial edema secondary to severe increase of the pericardial pressure, coronary venous congestion and impaired lymphatic drainage.

In 4 patients, the LV walls showed an increased echocardiographic reflectivity during cardiac tamponade as that found in infiltrative myocardial disease and in hypertrophic cardiomyopathy.⁸⁻⁹ Both mechanisms of LV pseudohypertrophy suggested before, namely myocardial congestion with edema and compression of myocardial fibers, may be compatible with this echocardiographic appearance.

LV pseudohypertrophy should be suspected when pericardial effusion is associated with increased LV wall thickness. This is an important finding, since it implies the presence of cardiac tamponade that was found in each of our patients. In one of our patients, this was the only echocardiographic finding associated with tamponade, apart of course from the finding of pericardial fluid. Factors that help in suspecting LV pseudohypertrophy are the following: no history or evidence of an underlying disease causing severe LV hypertrophy; the presence of clinical and echocardiographic signs of cardiac tamponade; and the knowledge of a previous or recent echocardiogram with normal LV wall thickness.

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Detection of Microbubbles Released by Oxygenators During Cardiopulmonary Bypass by Intraoperative Transesophageal Echocardiography

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Despite the improvements in cardiopulmonary bypass techniques, release of microbubbles in the systemic arterial circulation still occurs. It is believed that microemboli, prolonged arterial hypotension, defective cerebral blood flow autoregulation and nonpulsatile flow during cardiopulmonary bypass play a role in determining neurologic damage after cardiopulmonary bypass.^{1,2} Gaseous and particulate microemboli may originate from the pump-oxygenator system as well as from the cardiac chambers and pulmonary veins.^{1,3} In this study, transesophageal echocardiography was used to detect microbubbles reaching the arterial circulation during cardiopulmonary bypass. Two different types of oxygenators (bubbles and hollow fibers) were used to assess differences in their production of microbubbles.

Transesophageal echocardiography was performed in 20 patients undergoing various types of open-heart surgery (Table I). Esophageal disease was carefully excluded on the basis of history and preoperative esophagogram. Each patient gave informed consent for this procedure before the operation.

Transesophageal echocardiography was performed using a 5 MHz phased-array transducer (Hewlett-Packard model 21362 A), connected to a Hewlett-Packard ultrasonograph (model 77025 A). After the induction of anesthesia and tracheal intubation, the ultrasound probe was introduced blindly into the esophagus with the patient in the supine position. After having advanced the transducer into the esophagus to image the left atrium in the 4-chamber view, the ultrasound probe with the flexion locking device off was rotated counterclockwise to obtain a cross-sectional view of the descending aorta. From this position, the ultrasound probe was pulled back to visualize the upper portion of the descending aorta. Two-dimensional recordings of the descending aorta were made at the following times: immediately

before starting cardiopulmonary bypass; during the first 10 minutes of cardiopulmonary bypass before systemic hypothermia; at 30-minute intervals for 30 seconds during the rest of cardiopulmonary bypass; at the restoration of effective cardiac contraction; and after the end of cardiopulmonary bypass. When transesophageal imaging was not being performed during the hypothermic phase of cardiopulmonary bypass, the ultrasound probe was disconnected from the echocardiographic unit to avoid useless increase of the surface temperature at the distal tip.⁴

After a standard median sternotomy, atrial (or bicaval) and aortic cannulation were performed; a needle vent was placed in the ascending aorta. A hollow-fiber oxygenator (Terumo Capiox E) was used in 10 patients and a bubble oxygenator (Dideco D700) in the remaining 10. The same roller pump and aortic cannulas (Sarns model, size 24Fr) were used in all patients. Cardiomy suction was kept to a minimum to avoid gross entry of air in the circuit. An arterial filter was never used. A crystalloid priming solution was always used and priming of the system was performed at a slow rate through the cardiomy reservoir to minimize microbubbles production. Moderate systemic hypothermia (28°C) was used in all patients with flow rates between 1.8 and 2.4 liters/min/m². The intracardiac repair was performed during a single period of aortic cross-clamping. Cold hyperkalemic cardioplegia was used for myocardial protection, as well as topical hypothermia with cold saline irrigation. Rewarming was performed with a temperature gradient <10°C. To exclude damage of the esophageal mucosa (i.e., esophageal burns), possibly occurring during hypothermia, esophagoscopy was performed by an experienced endoscopist within 24 hours of surgery in 6 patients.

At the start of the cardiopulmonary bypass, infusion of priming solution in the arterial circuit produced a cloud of echoes within the lumen of the descending aorta (Figures 1 and 2). This phenomenon reflected the mixture of differently dense fluids, the priming solution and the patient's blood. Depending on the speed used to reach

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TABLE I Different Microbubbles Released by Oxygenators During Cardiopulmonary Bypass

Pt No.	Age (yr)	Gender	Pump	Oxygenator	Priming EC (s)	MBL		Surgery
						Early (s)	Throughout CPB	
1	54	M	Roller	Hollow fibers	100	130	0	CABG, MV repair
2	32	M	Roller	Hollow fibers	10	60	0	MV replacement
3	61	M	Roller	Hollow fibers	43	214	0	MV replacement
4	49	F	Roller	Hollow fibers	9	88	0	AV replacement
5	64	F	Roller	Hollow fibers	30	177	0	CABG, AV replacement
6	48	F	Roller	Hollow fibers	34	114	0	AV, MV replacement
7	60	M	Roller	Hollow fibers	20	76	0	VSD closure
8	56	M	Roller	Hollow fibers	34	120	0	CABG
9	66	M	Roller	Hollow fibers	35	30	0	CABG
10	52	F	Roller	Hollow fibers	20	90	0	AV, MV replacement
11	57	M	Roller	Bubbles	35	+	+	AV replacement
12	53	M	Roller	Bubbles	20	+	+	MV replacement
13	68	M	Roller	Bubbles	86	+	+	CABG
14	52	F	Roller	Bubbles	34	+	+	MV replacement
15	35	M	Roller	Bubbles	52	+	+	MV commissurotomy
16	58	F	Roller	Bubbles	22	+	+	AV replacement
17	50	F	Roller	Bubbles	45	+	+	MV commissurotomy
18	68	F	Roller	Bubbles	38	+	+	CABG
19	61	F	Roller	Bubbles	30	+	+	CABG
20	68	F	Roller	Bubbles	75	+	+	MV replacement

AV = aortic valve; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; EC = echocardiographic contrast; MBL = microbubbles; MV = mitral valve; VSD = ventricular septal defect; 0 = MBL absent; + = MBL visible.

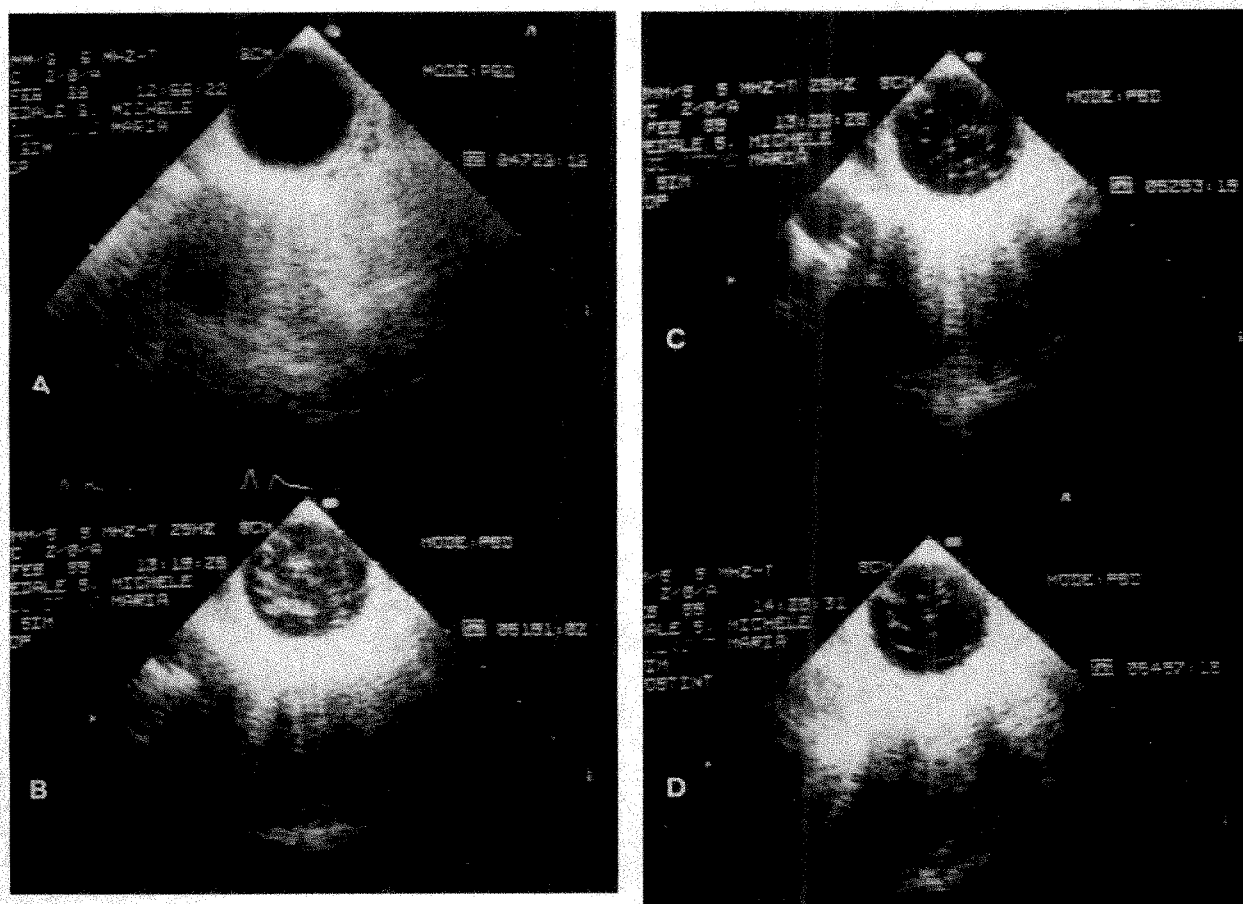


FIGURE 1. Bubble oxygenator. **A**, trans-esophageal cross-sectional view of descending aorta before start of cardiopulmonary bypass. **B**, echocardiographic contrast during infusion of priming solution at start of cardiopulmonary bypass. **C, D**, appearance of microbubbles lasting throughout cardiopulmonary bypass.

a full-flow bypass, it lasted 9 to 100 seconds (38.6 ± 23.8 seconds [mean \pm standard deviation] Table I).

After this echocardiographic contrast, microbubbles appeared as oblong bright particles with continuous, fast and circular movement. When bubble oxygenators were used, microbubbles were seen in the descending aorta throughout cardiopulmonary bypass (Figure 1). Their number seemed directly related to the flow. Conversely, with hollow-fiber oxygenators, the release of microbubbles was confined to the early phase of cardiopulmonary bypass after the infusion of the priming solution and lasted 30 to 214 seconds (110 ± 54.5 seconds [mean \pm standard deviation], Figure 2, Table I). In addition, microbubbles originating from infusion of blood or drugs into the arterial circuit, as well as from the left cardiac chambers at restarting of effective cardiac contraction, were also seen transiently in the descending aorta during cardiopulmonary bypass. These microbubbles appeared transiently when hollow-fiber oxygenators were used and were superimposed on those coming from bubble oxygenators. Strong suction applied to the aortic needle vent helped evacuate those coming from the heart.

Postoperative endoscopy did not show evidence of significant esophageal lesions in any patient.

Although accurate surgical technique may avoid embolization of organic material from the left cardiac chambers, gaseous microemboli coming from the surgical field at restarting of effective cardiac contraction are much more difficult to eliminate and may be as dangerous. Transesophageal echocardiographic monitoring of air at this stage can minimize its harmful effects by allowing discontinuation of cardiopulmonary bypass only after complete evacuation of air from the cardiac chambers.^{4,5} Air can be generated in several points of the pump-oxygenator system at different stages of cardiopulmonary bypass. In this study, we evaluated the role of 2 different types of oxygenators in microbubble production. We therefore tried to minimize the influence of all other known causes of microbubble production by standardizing the cannulation technique and cardiopulmonary bypass conduction.

Our results show that the time-course of aortic microbubbles varies in relation to the type of oxygenator used. Gaseous microemboli were seen in the descending aorta

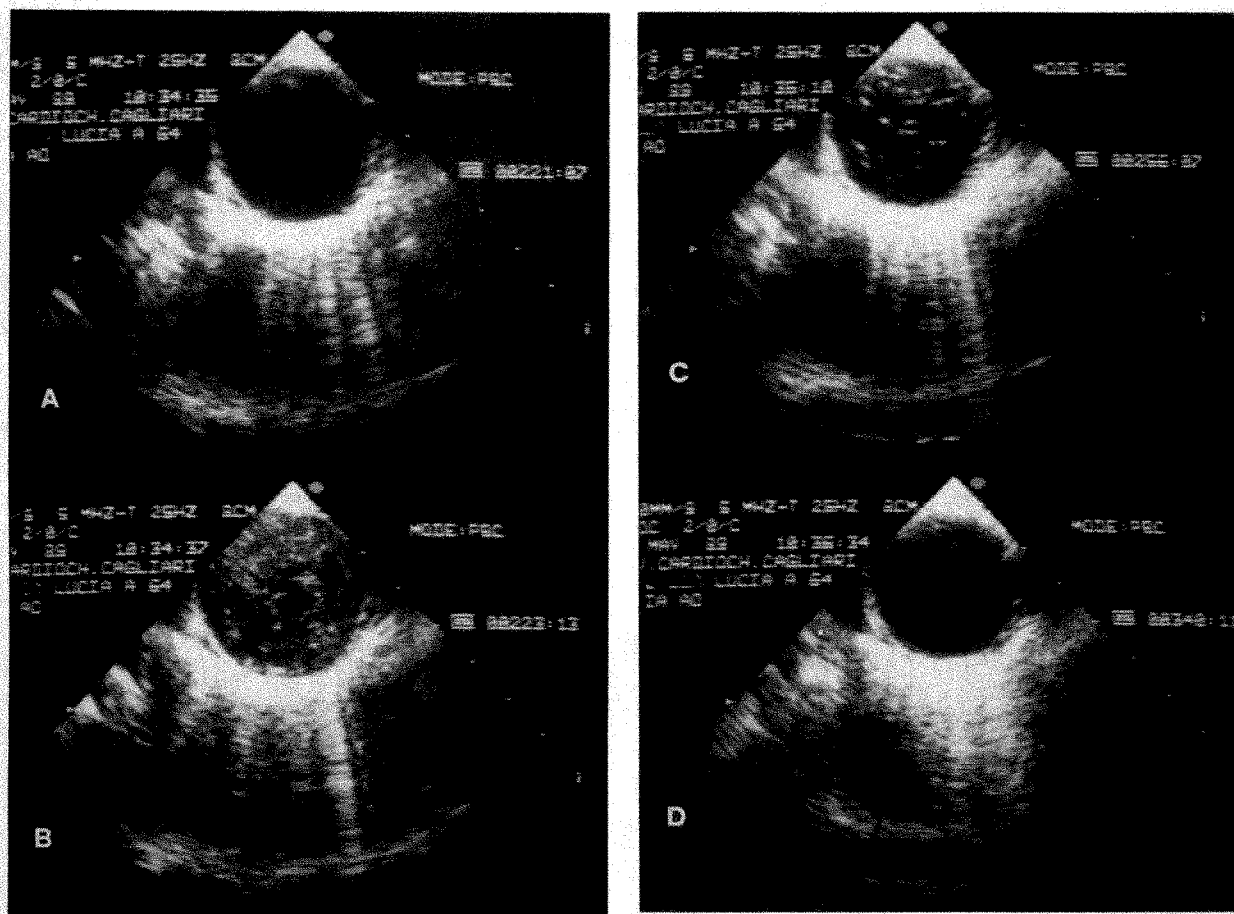


FIGURE 2. Hollow-fiber oxygenator. **A**, transesophageal cross-sectional view of descending aorta before start of cardiopulmonary bypass. **B**, echocardiographic contrast during infusion of priming solution at start of cardiopulmonary bypass. **C**, appearance of microbubbles during early phase of cardiopulmonary bypass. **D**, disappearance of microbubbles after early phase of cardiopulmonary bypass.

throughout cardiopulmonary bypass when bubble oxygenators were used, thus confirming the findings obtained with microbubble activity monitors.¹ Moreover, even though a specific search was not performed, the number of microemboli seemed directly related to the pump flow. Conversely, when hollow-fiber oxygenators were used, microbubbles were only visualized within the first few minutes of cardiopulmonary bypass after the infusion of the priming solution. It remains to be verified whether other types of membrane oxygenators may be even more effective in eliminating microbubbles.

In view of our findings, an arterial filter should be incorporated into the cardiopulmonary bypass circuit, especially when bubble oxygenators are used. This would

eliminate or significantly decrease the number of oxygenator-generated microbubbles reaching the arterial circulation.

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Unsolicited Medical Journals

Howard R. Horn, MD

The proliferation of medical mailings has skyrocketed in recent years and now approaches overwhelming proportions for busy American cardiologists. The majority of such "literature" is unsolicited and much of it appears to be published for mostly financial considerations. While all physicians receive a number of unsolicited medical journals in the mail, it is my impression that cardiologists lead the pack in the number received. To obtain a realistic assessment of this number, a count was made of all medical publications received in the mail during a single month in 1989. The titles of these journals and mailings with dates received are listed in Table I. As seen in this Table, both the total number of mailings and those received on a single day are astounding! A cardiologist receiving 9 journals on 1 day is probably receiving more than many physicians in other specialties receive in a week or even a month. Even more astounding is the observation that of 108 total pieces of medical mail received during 1 month, 88% was unsolicited.

An interesting paradox is provided by the aforementioned numbers. Cardiologists, probably the busiest specialists in our society, now appear to be the ones also bearing the brunt of the proliferation of unsolicited medical literature. The conscientious cardiologist striving to keep up with the literature may feel compelled to read or scan these unsolicited items, creating further demands on already limited time. To deal with this unwieldy task, some cardiologists may have to develop novel approaches. One approach that I have periodically adopted entails keeping journals in the back seat of the car so they are conveniently available to scan and then discard anytime, anywhere!

Finally, most of the articles in the unsolicited journals are written by physicians and some are published by publishers seeking profit only. It might be wiser for physi-

cians to spend their writing energies on peer-review publications that end up on library shelves rather than on throwaways that end up in trashcans.

TABLE I Medical Journals and Mailings Received on a Daily Basis From May 15, 1989 to June 15, 1989

May 15	Annals of Internal Medicine
Drug Therapy	ACC Convention Reporter
Consultant	C-V News
Emergency Medicine	AHA Focus Series—
Human Sexuality	Hypertension
Hospital Practice	Side Streets
American Medical News	Medical Tribune
May 16	Post-Graduate Medicine
Clinical Symposia	Internal Medicine World
Medical Tribune	Report
New England Journal of	May 24
Medicine	Acute Care Therapeutics/
American Journal of	ACT
Cardiology	American Medical News
Clinical Cardiology	Myocardial infarction—
M.D. Magazine	Rationale for Rx-Highlights
Cardiology Product News	of University of Florida
Cortlandt Forum	Conference
Choices in Cardiology	Mayo Clinic Proceedings
May 17	Internal Medicine for the
Cardiology	Specialist
CV Reviews & Reports	May 25
May 18	Cleveland Clinic Journal of
Ca-A Ca Journal for Clinicians	Medicine
May 19	Geriatric Medicine Today
Physicians & Computers	New England Journal of
Primary Cardiology	Medicine
May 20	National CV Bulletin
Physicians' Travel & Meeting	May 26
Guide	Emergency Medicine
Monthly Prescribing	Memphis Health Care News
Reference	Internal Medicine News
May 22	Report of Chatham Meeting—
Physicians' Financial News	CHF/New Approaches to Rx
CARDIO	Hospital Practice
Physicians' Lifestyle Magazine	CV Rounds
May 23	May 27
Cardiology	Medical Electronics

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TABLE I (continued)

Equipment News	VARIA	Medicine	Medicine World News
American Journal of Cardiology	PRN-Frontline Report	June 9	American Heart Journal
May 29 and 30	June 3	Human Sexuality	Annals of Internal Medicine
New England Journal of Medicine	Medical Tribune	Diversio	Directory for the 90's
Journal of Cardiac Rehabilitation	June 5	Arrhythmia Clinic	Medical Tribune
Medical World News	Cardiology World News	Council for Tobacco Research	Emergency Medicine
Today in Medicine	The Physician & Sports Medicine	Clinical Cardiology	Archives of Internal Medicine
Physicians Financial News	Cardiology Medical News	Memphis Health Care News	Practical Cardiology
June 1	June 6	The Journal of Myocardial Ischemia	Journal of the National Medical Association
American Medical News	American College of Physicians Observer	June 10	June 14
Senior Patient	Journal of the American College of Cardiology	Private Practice	Preventive Cardiology '89
News—From the CV Center of Emory University	American Journal of Cardiology Symposium	American College of Cardiology—Annual Scientific Session	Physicians Management
Your Patient & Fitness in Cardiology	June 7	News	Modern Medicine
Mg ⁺ Alert Line	Monthly Prescribing Reference	LeBonheur News	Internal Medicine World Report
June 2	Omni Medical	Hospital Medicine	June 15
Internal Medicine News	Contemporary Internal Medicine	The Journal of Clinical Illness	Physicians Market Place
New Bulletin—ACC 38th Annual Session	New England Journal of Medicine	June 12 and 13	ACC Cardiology
		Physicians Financial News	New Horizons for the Physician-M.D.
		New England Journal of Medicine	Hospital Practice

Total pieces of medical mail in 1 month = 108.
% medical mail unsolicited = 88.

Effect of Altered Flow on Mitral Valve Anulus in Dogs

Byron F. Vandenberg, MD, and Richard E. Kerber, MD

Stroke volume and cardiac output are accurately estimated by Doppler echocardiographic methods that rely on inflow velocities and orifice area of the mitral valve.^{1,2} Changes in inflow velocities represent changes in flow, but this requires the assumption of a stable mitral anulus area. It is known that the anulus area decreases by an estimated 20 to 50% during systole,^{3,4} but there are few data on the effect of altered filling on the anulus. This study determines the effects of flow increased with dobutamine or decreased with phenylephrine on the mitral anulus.

We studied the effects of altered flow on the mitral anulus in 10 dogs that were part of another study. The dogs were anesthetized with sodium thiopental 30 mg/kg intravenously, intubated and ventilated. Catheters were inserted in the femoral arteries for monitoring blood pressure and in the veins for administering fluids and medications. The dogs were allowed to recover for at least 72 hours. Before echocardiographic study, they were sedated with 0.2 to 0.4 ml of Innovar-Vet (fentanyl citrate and droperidol, Taylor Pharmaceutical Co.) intravenously.

Two-dimensional echocardiography was performed with an Advanced Technology Laboratories Ultramark

8 ultrasonoscope. With the dogs laying on their right sides, the parasternal long-axis view was obtained with a 5 mHz transducer. The animals were then turned onto their left sides and mitral inflow velocities were recorded using Doppler echocardiography. Positioning dogs on their left sides permitted optimal visualization of a 4-chamber apical view. The Doppler ultrasound beam was

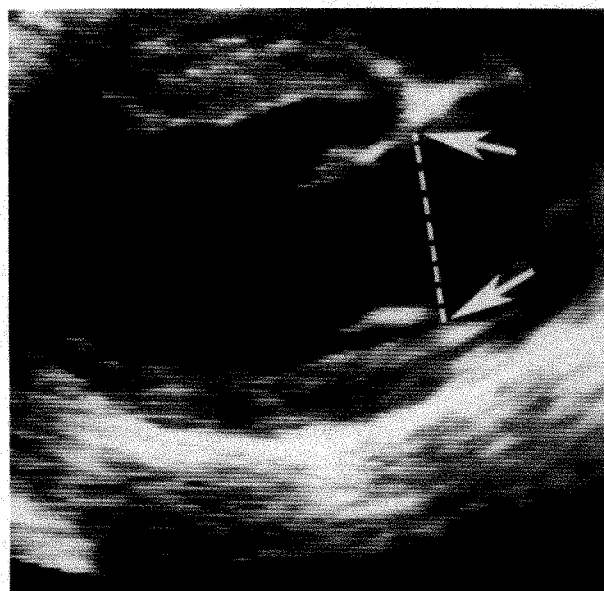


FIGURE 1. Parasternal long-axis view of left ventricle. Arrows indicate insertion points of mitral leaflets.

From the Cardiovascular Center, Department of Internal Medicine, University of Iowa College of Medicine, Iowa City, Iowa 52242. This study was supported in part by a grant-in-aid (Dr. Vandenberg) from the Iowa Affiliate of the American Heart Association, Des Moines, Iowa. Manuscript received November 27, 1989; revised manuscript received April 9, 1990, and accepted April 10.

TABLE I Hemodynamics and Left Ventricular Dimensions During Dobutamine and Phenylephrine Infusion

	Mean BP (mm Hg)	HR (beats/min)	LVEDD (cm)	LVESD (cm)	Fractional Shortening (%)	Velocity Time Integral
Control 1	113 ± 10	83 ± 23	3.1 ± 0.3	1.8 ± 0.2	0.41 ± 0.09	6.6 ± 1.2
Dobutamine	125 ± 15*	99 ± 24*	3.2 ± 0.3	1.6 ± 0.4*	0.52 ± 0.12*	7.9 ± 1.7*
Control 2	107 ± 14	76 ± 18	3.2 ± 0.3	1.8 ± 0.4	0.44 ± 0.11	7.2 ± 1.7
Phenylephrine	153 ± 22*	62 ± 14	3.4 ± 0.3*	2.1 ± 0.3*	0.38 ± 0.09*	5.9 ± 1.1*

* $p < 0.05$ vs control.

BP = blood pressure; HR = heart rate; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter.

TABLE II Mitral Anulus Diameter During Dobutamine and Phenylephrine Infusion

	Mitral Anulus Diameter (cm)		
	Early Diastole	Late Diastole	% Change
Control 1	1.8 ± 0.2	2.0 ± 0.1	-12 ± 9
Dobutamine	1.7 ± 0.2	1.8 ± 0.3	-5 ± 7
Control 2	1.8 ± 0.3	2.0 ± 0.3	-7 ± 6
Phenylephrine	2.0 ± 0.3	2.0 ± 0.2	-2 ± 9

p = difference not significant.

thus oriented parallel to left ventricular inflow. After baseline recordings, dobutamine 10 $\mu\text{g/kg/min}$ was infused intravenously. Two-dimensional and Doppler echocardiography recordings were repeated. After 15 minutes, the infusion was increased to 20 $\mu\text{g/kg/min}$ and recordings were repeated. The dobutamine was then discontinued and, after 1 hour, additional control recordings were obtained. Innovar-Vet 0.1 to 0.2 ml was administered intravenously again. Phenylephrine was then administered intravenously in doses of 5, 10 and 25 $\mu\text{g/kg/min}$ until systolic arterial pressure increased by at least 30 mm Hg above the baseline. Two-dimensional and Doppler echocardiography were then repeated.

The mitral anulus diameter was measured off-line using an average of 3 beats. The anulus was identified as the point of insertion of the mitral valve leaflets (Figure 1). Diameters were measured twice: in early diastole (after the valve leaflets had opened to full excursion) and in late diastole (just before valve leaflet closure). The percent change in diameter relative to early diastole was calculated. The velocity-time integral of the mitral inflow was planimtered from Doppler recordings. In addition, left ventricular end-diastolic and end-systolic dimensions were measured from m-mode echocardiographic recordings of the left ventricle. These dimensions were averaged from 10 beats and fractional shortening was calculated.

Differences in observations from first control to dobutamine and second control to phenylephrine were evaluated by paired *t*-tests. Data are expressed as mean \pm standard deviation.

Dobutamine produced an increase in fractional shortening and velocity-time integral compared to control (Table I). However, there were no significant changes in mitral anulus diameters or in relative changes of diameter compared to control (Table II).

With phenylephrine administration, percent fractional shortening and velocity-time integral decreased compared to control. Again, neither mitral anulus diameter nor relative change in diameter changed compared to control.

We found that changes in flow produced by dobutamine and phenylephrine did not change the mitral anulus diameter. Rassi et al⁵ demonstrated an increase in mean diastolic mitral orifice area of 29 to 34% without changes in the velocity-time integral during exercise. Exercise, however, produces multiple hemodynamic alterations, including increased preload and contractility, as well as decreased vascular resistance.⁶ Selective increases in preload and decreases in afterload were not addressed in our study, but may have been responsible for the changes in the anulus noted during exercise by Rassi et al.

We also demonstrated insignificant changes of the anulus diameter during acute increases in systolic blood pressure with phenylephrine infusion. Doppler echocardiographic measurements of diastolic filling velocity have been used to study left ventricular function in hypertensive patients.⁷ Our data support the use of serial filling velocity measurements to assess changes in flow, since increases in arterial pressure may not alter the anulus.

A potential limitation of our study is the use of a single dimension measurement of the mitral anulus to draw conclusions about anular geometry. Previous echocardiographic studies of the mitral anulus have used apical 4-chamber views with recordings made at 30° rotational intervals. Ormiston et al⁴ demonstrated a change in area of $26 \pm 3\%$ during the cardiac cycle in normal subjects when each of the chords from the rotational intervals was arranged around a reference point. Vijayaraghavan et al⁸ compared a simplified 2-plane method of calculating the mitral anulus area with the more detailed 30° rotational method and the areas were nearly identical ($r = 0.98$). The 2-plane method required orthogonal views provided by parasternal long axis and 4-chamber apical plane. In our study, 4-chamber apical views were obtained, but during dobutamine infusion the points of leaflet insertion into the anulus were not clearly identified. Thus, we were limited to a single imaging view. In addition, dogs were moved between interventions and therefore transducer position may have varied slightly. We attempted to minimize this variability using constant interspaces and anatomic landmarks.

In summary, the mitral anulus diameter is not significantly changed by interventions that alter flow. This provides a rationale for the use of serial Doppler echocardi-

graphic studies to evaluate changes in mitral inflow velocities that may be taken to reflect actual flow changes given a stable mitral annulus.

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Abstracts

American Academy of Pediatrics
Section on Cardiology
32nd Annual Meeting
Boston, Massachusetts
October 5-7, 1990

The following abstracts were selected for oral presentation in a peer-review process by the Executive Committee of the Section on Cardiology, American Academy of Pediatrics. The first 6 abstracts were selected as finalists in the Young Investigator Award Competition.

Abstracts 1 through 18 will be presented on Saturday, October 6, and abstracts 19 through 38 on Sunday, October 7.

1

DIFFERENCES IN CARDIAC CONTRACTILE PROTEINS: EMBRYONIC TO ADULT LIFE. Thomas J. L'Ecuver, FAAP* and Jim J.C. Lin, Department of Pediatrics, University of Iowa, Iowa City, IA

Neonatal and adult myocardium respond differently to stimuli, e.g. inotropes and acidosis, likely related to the profile of contractile proteins present on the developing microfilament. We examined the isoform changes in developing rat hearts by Western blot. In addition, we immuno-precipitated developing thin filaments with an antibody to tropomyosin, and analyzed them as an index of function of embryonic isoforms of troponin T (TnT) and I (TnI). We identified adult and embryonic cardiac TnI isoforms and a skeletal muscle isoform, all with different molecular masses. TnI isoform switching begins by embryonic day 16 and is completed by postnatal day 21. TnT isoform switching begins after birth and is complete by postnatal day 15. TnT but not TnI isoform switching is demonstrated on immuno-precipitated thin filaments during perinatal heart development. The timing of isoform switching and presence of embryonic TnT but not TnI on developing thin filaments suggests that TnT may play a greater role in determining developmental differences in myocardial function. In addition, 2D gel electrophoresis demonstrates that the extent of phosphorylation of tropomyosin decreases significantly as development progresses. This change may be responsible for some of the observed functional differences seen in developing hearts.

2

ANGIOTENSINOGEN (AO) GENE REGULATION IN THE PREGNANT AND FETAL RAT Allen D. Everett*, Robert L. Chevalier, and R. Ariel Gomez. Department of Pediatrics, University of Virginia, Charlottesville Virginia.

Ao, is the only known precursor of angiotensin II, a potent regulator of blood pressure and fluid-electrolyte homeostasis. Expression of the fetal Ao gene is developmentally regulated, increasing markedly at birth. To determine whether expression of the Ao gene is hormonally regulated in the pregnant and fetal rat, time dated pregnant Wistar-Kyoto rats were given either a daily intraperitoneal injection of dexamethasone (Dex, 10mg/kg) or T3 (10ug/kg) for five days (chronic Dex or T3) and sacrificed on day 20 of gestation or a single injection of Dex on day 20 of gestation and sacrificed after six hours (acute Dex). Total RNA from maternal and fetal livers, brains, kidneys and hearts was extracted and Ao mRNA levels determined by dot and Northern blot hybridization using a rat ³²P-Ao cDNA. Chronic Dex treatment resulted in a 190% increase in maternal and 370% increase in fetal hepatic Ao mRNA levels, without affecting Ao mRNA levels in the fetal brain, heart or kidney. Acute Dex treatment resulted in a 260% increase in maternal hepatic Ao mRNA levels with no change in the fetus. In addition, baseline hepatic Ao mRNA levels were decreased 250% in pregnant animals as compared to non-pregnant females and males. Chronic T3 treatment resulted in a 20% increase in maternal hepatic Ao mRNA levels, without alteration of fetal Ao gene expression. We conclude that: 1) Ao gene expression is regulated by glucocorticoids in the term fetal and maternal liver; 2) Although the Ao gene is expressed in multiple fetal organs, the response to Dex is tissue specific. 3) Contrary to previous enzymatic studies hepatic Ao gene expression is reduced during pregnancy and 4) Chronic T3 treatment results in a modest increase in maternal hepatic Ao gene expression. The augmentation of fetal Ao gene expression at term suggests that Ao may play an important role in preparing for the transition to extrauterine life.

3

MAGNETIC RESONANCE IMAGE-BASED CALCULATION OF T2 RELAXATION TIMES: POTENTIAL FOR NONINVASIVE MYOCARDIAL TISSUE CHARACTERIZATION. *T.D. Scholz, F.A.A.P., J.C. Ehrhardt, D.J. Skorton. Dept. of Pediatrics, Univ. of Iowa.

We have shown increased myocardial collagen content in hypertrophy and infarction is associated with longer in vitro T2 relaxation times (T2). Controversy exists as to whether magnetic resonance (MR) image-based calculations can accurately identify these small changes of T2. Since right and left ventricular (RV and LV) myocardial T2 are known to be different, we compared image-based T2 measurements with in vitro calculations and related differences in T2 to tissue water, fat and collagen content.

Spin-echo MR image intensities at 1.5 Tesla were used to calculate image-based T2 in the RV and LV free walls of 9 ex vivo hog hearts. Following imaging studies, in vitro T2 were determined at 0.47 Tesla. Tissue water, fat and collagen contents were determined on each in vitro sample.

Both image-based and in vitro T2 were significantly longer for the RV than the LV (image RV vs. LV = 59.0 ± 2.9 vs. 54.2 ± 3.6 msec and in vitro RV vs. LV = 68.1 ± 4.9 vs. 64.2 ± 5.0 msec; both $p < .001$). Further, RV water and collagen content were significantly greater than LV while fat content was not different. For the pooled RV and LV data, image-based T2 correlated with in vitro T2 ($r = 0.81$; $p < .0001$).

Conclusions: Image-based T2 measurements can identify small differences such as those that exist between the RV and LV. These image-based T2 calculations may allow noninvasive characterization of myocardial changes, such as occur in hypertrophy, cardiomyopathy, and infarction.

4

MATURATIONAL CHANGES IN FORCE DEVELOPMENT IN RABBIT PULMONARY ARTERY Jay S Chandar*, Amelia Escobar, Cornelis van Breemen, Henry Gelband, FAAP. Dept of Ped., Univ. of Miami, Miami, FL.

Maturation changes in the delivery of myoplasmic free calcium (Ca^{2+}) via transmembrane Ca channels (CH) and release from intracellular Ca stores (SR) were studied by measuring isometric force development (F), in newborn (N) ($n=6$), age 2-3 days, juvenile (J) ($n=6$), age 1 month, and adult (A) ($n=6$) rabbit pulmonary artery smooth muscle (PSM). Maintained tone due to receptor operated CH (ROC) was measured in the presence of norepinephrine 10^{-5} M (NE) and diltiazem 10^{-5} M. Tone due to voltage gated CH (VGC) was recorded in the presence of K^+ 80 mM and adrenergic blockers. SR Ca release was recorded as NE and caffeine 40 mM (CAF) contractions in the absence of extracellular Ca. The results for mean \pm F (gm/mm²) and % F (using VGC F as control) in each group are listed.

AGE	VGC	ROC	SR(NE)	SR(CAF)
N	$0.4 \pm .03^*!$	$0.14 \pm .02^*!$	$0.19 \pm .02^*!$	$0.04 \pm .01^*!$
% 100		$32.7 \pm 4.0^*!$	$48.1 \pm 8.3^*!$	$11.0 \pm 3.5^*!$
J	$3.1 \pm .29$	$2.4 \pm .15$	$2.3 \pm .22^*$	$0.5 \pm .06$
% 100		79.3 ± 6.6	$74.9 \pm 5.7^*$	15.7 ± 1.9
A	$3.3 \pm .32$	$2.4 \pm .29$	$4.2 \pm .46$	$0.8 \pm .13$
% 100		78.4 ± 16	128.1 ± 9.3	24.5 ± 3.5

* = N or J vs A $p < .05$; ! = N vs J $p < .05$.

F was higher in J & A compared to N with all stimulations. Compared to VGC stimulated F (100%) in each age group, % F was higher on ROC stimulation in J & A compared to N; and % F was progressively increased from N to A with release of SR Ca. Reported differences in pulmonary hypertension between N & A may be due to the above maturational changes in PSM Ca ion kinetics.

5

HYPEROXIA STIMULATES THE PRODUCTION OR RELEASE OF ENDOTHELIUM-DERIVED RELAXING FACTOR (EDRF) FROM NEONATAL VESSELS

Ronald W. Day*, Thomas S. Klitzner, and Louis J. Ignarro
Department of Pediatrics, UCLA

To determine whether oxygen (O2) stimulates the production or release of EDRF, the response of neonatal rabbit aortic (Ao) rings to an inhibitor, N-monomethyl-L-arginine (L-NMMA), was evaluated during mild hypoxia and hyperoxia. Following euthanasia with pentobarbital, the descending Ao was isolated and two Ao rings, with intact endothelium (E+), were mounted to an isometric tension transducer in separate baths of Krebs solution with 95% N2/5% CO2 (N2) [PO2 = 50-70 mmHg]. At steady baseline tension, L-NMMA, 0.001M, was added to one bath (A) and the response observed. Both vessels were then exposed to a gas mixture of 95% O2/5% CO2 (O2), [PO2 > 500 mmHg], and allowed to constrict maximally over 1-3 hours. Thereafter, the Ao ring of the second bath (B) was treated with L-NMMA, 0.001M, and the change in tension measured. O2-mediated constriction of endothelium-denuded (E-) Ao rings was also evaluated and the contractile response compared with E+ vessels using an unpaired t test.

Results: Experimental Condition/Ao Ring Tension (gm):

Ao	n	N2	N2/L-NMMA	O2	O2/L-NMMA
E+/A	6	0.95	0.95		1.65
E+/B	7	0.95		1.25	1.55
E-	6	1.00		1.55	1.55

L-NMMA did not change Ao (E+/A) tension during N2. However, a marked increase in Ao (E+/B) tension occurred when L-NMMA was added during O2. The contractile response of E- rings was not influenced by L-NMMA, confirming successful removal of the endothelium. Statistically comparable tensions were achieved by each Ao ring group following O2 and L-NMMA. Preliminary studies using piglet pulmonary arteries demonstrate an identical EDRF response to O2. Furthermore, indomethacin did not markedly influence tension during N2 or O2 in separate studies.

Conclusion: O2 stimulates the production or release of EDRF in neonatal rabbit and piglet vessels.

Perhaps, EDRF contributes to pulmonary vasodilation associated with alveolar hyperoxia.

6

ACUTE ADMIODARONE AFFECTS THE LOWER AV NODE IN NEONATAL AND ADULT RABBITS. *Charles H. Gaymes, Kenneth W. Hewett and Paul C. Gillette. Medical University of SC, Charleston, SC.

The effects of acute superfusion of amiodarone (AMIO) on neonatal (< 10 days of age) and adult rabbit atrioventricular node (AVN) preparations were studied using standard microelectrode techniques and surface electrograms. Pre-drug measurements, followed by drug measurements were made at stimulus cycle intervals of 400, 600, and 800 msec. AMIO (1×10^{-5} M) produced no significant change in any action potential characteristic in the upper regions of the AVN in either age group. In both neonate and adult, this drug significantly reduced the action potential upstroke velocity (V_{max}) of the lowest region of the AVN. The reduction in V_{max} was from 75.2 to 47.5 V/s (-37%) in neonatal preparations ($n=5$) and from 62.1 to 33.1 V/s (-46%) in the adult preparations ($n=6$). These drug induced changes in V_{max} demonstrated no cycle length dependence in either age group. There was a small but consistent reduction in action potential duration at 50 and 90% of repolarization in both age groups.

In conclusion, the primary effect of acute administration of AMIO on the AV node in neonates and adults is a reduction in V_{max} in the lower region.

7

PATTERNS OF ANOMALOUS PULMONARY VENOUS CONNECTION/DRAINAGE IN HYPOPLASTIC LEFT HEART SYNDROME. SURGICAL IMPLICATIONS AND DIAGNOSTIC ROLE OF COLOR DOPPLER. Mohamed Selim*, FAAP, Alvin Chin, William Norwood. The Children's Hospital of Philadelphia, Pennsylvania.

Pre-operative identification of precise connection and drainage of the pulmonary veins (PV's) in hypoplastic left heart syndrome (HLHS) is surgically important either with creation of a large ASD (Norwood's procedure) or when heart transplantation is contemplated. Echocardiography (ECHO) with color flow Doppler (CFD) of 217 patients (pts) with HLHS detected partial or total anomalous pulmonary venous connection in 15 pts (6.9%), all had absent or small foramen ovale, thick muscular atrial septum and/or posterior deviation of septum primum. In 10 pts, PV's were not connected to left atrium (LA) and drained anomalously to innominate vein (IV) (6 pts), superior vena cava (2 pts), coronary sinus (1 pt) and infracardiac (1 pt). In 2 pts, right PV's only were connected to the right side of the deviated atrial septum while left PV's were connected normally to LA. In 3 pts, all 4 PV's were normally connected to LA despite persistence of a vertical vein draining into IV. Echo with CFD defined the precise connection site of PV's in each case.

8

FETAL ECHOCARDIOGRAPHY - A COST-BENEFIT ANALYSIS David A. Danford, MD, FAAP*, Larry A. Latson, MD, FAAP, John P. Cheatham, MD, FAAP, Pediatric Cardiology, University of Nebraska Medical Center, Omaha, Nebraska

Fetal echocardiography (FE) has been advocated for many indications without quantitative discussion of anticipated costs (C) and benefits (B). The purpose of this investigation is to refine indications for FE by identification of clinical factors with major influence on C and B. Decision tree analysis revealed that of 13 variables that influence C and B, by far the most important was pre-FE probability of congenital heart disease (pCHD). Four others: financial cost of FE, duration of remaining pregnancy, value of parental reassurance by negative study, and anticipated change in one year survival due to recognition of heart disease in utero had large influences on C/B ratio. The remaining 8 variables had smaller impact. Even presuming a very high cost of FE and no anticipated benefit in parental quality of life, a minimal impact upon long-term survival of the fetus appears sufficient to justify FE, when pCHD > 10%. When pCHD < 5%, the impact on parental quality of life must be substantial to justify FE. The enthusiasm for FE must be tempered by the realization that under certain clinical circumstances (like when low pCHD and low impact on parental quality of life coexist), its C/B ratio does not compare well with that of other procedures with which it competes for the scarce medical dollar.

9

DOES LOW DOSE ASPIRIN AFFECT THE FETAL DUCTUS ARTERIOSUS?

*Ellen M. Weinstein, Kay Cox, Katherine C. Harris, Norman F. Gant, Ronald R. Magness. Dept. of Peds., UTSWMS, Dallas, TX

A decreased incidence of pre-eclampsia as well as improved fetal outcome in women on low-dose aspirin (ASA) has been reported. To evaluate the effects of ASA on the fetal ductus and potential morbidity, we performed serial fetal 2-D/Doppler echocardiograms (2D/DE) on 7 primigravid women receiving ASA, 81 mg/day, and on four normal women through the third trimester of pregnancy. 2D/DE was performed prior to ASA at 28±1wk gestation (G), and was repeated at 1 week and at 2-5 weeks of ASA, and in neonates. Peak systolic ductal flow velocity (DV) averaged 0.93 ± 0.06 m/sec prior to ASA (G24-33wk), 0.98 ± 0.05 m/sec after one week on ASA (G25-35wk), and tended to increase, 1.22 ± 0.11 m/sec ($p=0.06$) after 2-5 weeks on ASA (G27-37wk). DV were increased in association with both G and time on ASA. Two fetuses on ASA developed DV > 1.4 m/sec. In the normal women, DV tended to increase with advancing G, and was ≥ 1.4 in 3 of 4 patients in late gestation. The women on ASA had normal infants with normal post-natal 2D/DE and no evidence of pulmonary hypertension. It appears that increases in DV seen in patients on ASA may be related to advanced G, rather than ASA. Further, deleterious effects on the newborn due to ASA have not been demonstrated.

10

EXERCISE ECHOCARDIOGRAPHY (EE) FOR IDENTIFICATION OF ANTHRACYCLINE CARDIOTOXICITY

*Kenneth M. Weesner, M.D., FAAP, Marita Bledsoe, BS, Allen R. Chauvenet, M.D., Marcia Wofford, M.D. Pediatrics, Bowman Gray School of Medicine

In order to detect evidence of latent cardiomyopathy (C) in patients (pts) who received anthracyclines (A) for cancer chemotherapy we performed exercise echo (EE) on 20 asymptomatic survivors of childhood cancer (CC). 10 pts had received A, 10-20 yrs (m 14 yrs). These 10 had received $90-498 \text{ mg/m}^2$ of A (m 291) and were 4-13 yrs after treatment (m 7). 10 pts received no A, 8 to 27 yrs (m 16 yrs). Testing included resting M-mode, and Doppler Ao velocities. Exercise (EX) was with an upright bicycle ergometer. We recorded BP, HR, Ao peak velocity (AoPV) with each level of EX. Post-EX shortening fraction (% Δ), Vcf and AoPV were recorded. Mean CI was $5.7 \pm 1.6 \text{ L/min/m}^2$ in A pts and $5.5 \pm 1.3 \text{ L/min/m}^2$ in non-A pts ($p=NS$). After EX, CI was 11.4 ± 2.3 in A pts and 13.3 ± 4.4 in non-A pts ($p=.09$). (% Δ) changed from 39% \pm 8% to 38% \pm 8% after EX in the A pts and from 43% \pm 7% to 52% \pm 11% in the non-A pts ($p<.005$). Vcf changed from $1.3 \pm .3$ to $1.5 \pm .5$ in A pts and from $1.5 \pm .2$ to $1.8 \pm .5$ in non-A pts ($p=.05$). AoPV increased by $72 \pm 19 \text{ cm/sec}$ in A pts and by $124 \pm 60 \text{ cm/sec}$ in non-A pts ($p=.05$). We conclude that EE identifies subtle myocardial abnormalities in late survivors of CC who have received A.

11

THE USE OF LEFT VENTRICULAR FRACTIONAL SHORTENING AS AN INDEX OF CONTRACTILITY IN HIV-INFECTED CHILDREN. Steven E. Lipshultz, MD FAAP*, Stephen P. Sanders, MD, Steven D. Colan, MD, E. John Orav, PhD, Kenneth McIntosh, MD. Department of Cardiology, The Children's Hospital, Boston MA.

Left ventricular contractility in HIV-infected patients is an important measure of the extent of cardiac involvement and of the success of therapeutic interventions. However, load dependent ejection phase indices such as fractional shortening (FS), which are commonly utilized to determine contractility, may not provide accurate information about contractility. To assess this relationship we examined 176 echos from 74 HIV-infected children in which there were simultaneous measurements of FS, contractility (utilizing the rate-corrected velocity of fiber shortening - end-systolic wall stress relation: a validated, load-independent index), LV afterload and preload. As expected, FS and contractility showed a strong correlation ($r^2 = .84$). However, when FS was divided into depressed (<28%), enhanced (>34%) and normal ranges, it did not correctly predict contractility classification for many echos. Forty-two percent of echo studies with depressed FS had either normal (16/43) or enhanced (2/43) contractility. Enhanced FS predicted enhanced contractility in only 57% (48/84) of echos. Afterload was abnormal in 56% and preload was abnormal in 26% of all echos. Loading abnormalities explained most discrepancies between contractility and FS.

In summary, the high incidence of abnormal loading conditions in HIV-infected children precludes the use of load-dependent ejection phase indices, particularly FS, to assess contractile state. Measurement of load-independent contractility and specific loading conditions allows more accurate determination of clinical status and may lead to more rational clinical management of HIV-infected children.

12

COMPARISON OF TRANSESOPHAGEAL AND EPICARDIAL ECHOCARDIOGRAPHY IN SMALL CHILDREN DURING SURGERY FOR CONGENITAL HEART DISEASE. D.A. Fyfe, FAAP*, C.H. Kline, R.M. Sade, F.A. Crawford, C. Greene and N.H. Brahen, Medical University of South Carolina, Charleston, SC.

We compared intraoperative transesophageal (TEE) and epicardial (EPI) 2-D and color flow Doppler echocardiography during open heart surgery in 35 children aged from 1.5 to 41 (median 12) months and weighing from 3.6 to 16 (median 8) Kg. In optimal studies repaired regions were fully visualized and Doppler flow was diagnostic. Heart defects included, atrial (ASD) (6), ventricular (VSD) (7) and atrioventricular (AVSD) (4) septal defects, Tetralogy of Fallot (5). Eight patients had modified Fontan operations.

Optimal Studies

	ASD	AVSD	FONTAN	mVSD	oVSD	RVOT
TEE	6	4	6	1	2	1
EPI	5	1	2	4	5	5

m=membranous, o=outlet, RVOT=right ventricular outflow tract.

Limitations of TEE were regions far from the transducer e.g. RVOT or those masked by prosthetic material e.g. outlet VSD. TEE was superior to EPI for evaluation of cavo-pulmonary anastomoses, inlet anatomy and atrioventricular valve regurgitation. EPI was superior for anterior VSD and outflow tract assessment. Whether TEE or EPI are selected for intraoperative echo-Doppler assessment of surgical results should be based upon knowledge of the limitations of each technique in visualizing the specific lesion operated.

13

TRANSESOPHAGEAL COLOR FLOW IN CONGENITAL HEART DISEASE: A NEW PEEP HOLE TO THE HEART

Samuel B. Ritter, M.D., FAAP, Ped. Cardiology The Mount Sinai Medical Center, New York, NY

Transesophageal Doppler color flow echo (TEE) has gained importance in the evaluation of congenital heart disease. A prototype 5 MHz 6.8 mm phased array TEE probe was used (Aloka/Corometrics) to perform 83 studies in 65 infants and children ranging in age from 6 hours to 18 years (m - 32 m) weighing 2.4 - 30 kg (m - 10.6 kg). 29 of the patients were infants under 1 year of age: 18 were studied by TEE within the first 10 days of life (weight range 2.4 - 4.3 kg). Studies were performed both intra- and postoperatively. TEE was diagnostically critical in 21 infants, (33%) identifying structures not seen by standard transthoracic echo or cardiac catheterization. These included identification of confluent pulmonary arteries in 3 patients with pulmonary atresia, coronary artery anomalies in 5 infants with transposition and tetralogy, and straddling AV valve attachments in 2 infants with AV septal defects. The majority of infants underwent palliative or corrective surgery without cardiac catheterization based on TEE echo studies. 4 patients underwent reoperation based solely on TEE ICU studies. TEE is a safe diagnostic imaging modality whose use in the smallest infants is now a reality: it provides invaluable intra- and postoperative hemodynamic information in a "noninvasive" real time manner.

14

ABNORMAL NOREPINEPHRINE RESPONSE TO MAXIMAL EXERCISE IN HYPERTENSIVE COARCTECTOMY PATIENTS. Robert D. Ross MD, FAAP*, Sandra K. Clapp MD, FAAP, Stephen Gunther MD, Stephen M. Paridon MD, FAAP, Richard A. Humes MD, FAAP, Zia Q. Farooki MD, FAAP, William W. Pinsky, MD, FAAP. Cardiology-Children's Hospital of Michigan, Wayne State Univ. School of Medicine, Detroit, MI.

Since the mechanisms of exercise induced hypertension (HTN) after coarctectomy are not fully known, 34 patients aged 7.8-40.3 (median 15.4) years were studied with graded stress tests 4.4-25.0 (median 9.5) years after repair. Serial samples for plasma norepinephrine (PNE) were drawn from an indwelling venous catheter. **Results:** NT=Normotensive exercise response, RC=residual or recoarctation. **Peak PNE:**

	n	No RC	n	RC
NT	13	1708±653 pg/ml	7	2440±689
HTN	7	3077±1216*	7	2921±1132*

*=p<0.01 vs. NT/No RC by oneway ANOVA

Patients with exercise HTN also had higher resting, 5' and 15' post-exercise systolic BPs and 5' post PNE than the NT group. There were no differences in age, BSA, year of repair, HR, diastolic pressures, baseline PNE, maximal work rate, oxygen consumption, or respiratory quotient between the HTN and NT groups. **Conclusion:** Exercise induced HTN after coarctectomy is related to abnormal sympathetic output whether or not RC has occurred.

ABSTRACTS

15

SHORT TERM EFFECTS OF r-ERYTHROPOIETIN (EPO-EPOGEN) ON CARDIAC PERFORMANCE.

Gerard R. Martin¹ FAAP, Raymon J. Ongkingco, Mary E. Turner FAAP, Elaine S. Skurow, Edward J. Ruley FAAP. Department of Cardiology, Children's National Medical Center, Washington, DC.

To determine the hemodynamic effects of anemia in children with end stage renal disease (ESRD), we studied cardiac performance before and after EPO. Children were included if they required renal dialysis, were anemic and had normal blood pressure +/- Rx. EPO 50 U/kg IM/IV was given 3 times/week until Hct \geq 33%. Cardiac output (rebreathing), 2D echo and treadmill tests (Bruce Protocol) were performed. 5 boys and 5 girls, 15 \pm 3y, with ESRD (serum Cr 6.5 \pm 4.5mg/dl) were given EPO and Hct increased (21 \pm 3% to 33 \pm 3%, $p \leq 0.001$). Resting cardiac index was increased before EPO and decreased after EPO (4.69 \pm 1.20 to 3.17 \pm 0.45 l/min/kg, $p=0.016$) due to decreases in HR and stroke volume. Blood pressure did not change. Cardiac wall thickness, chamber dimensions, LV wall stress and velocity of circumferential fiber shortening were normal and did not change with EPO. Exercise time was decreased before EPO and increased to normal range (9.5 \pm 2.2 to 10.7 \pm 1.6 min, $p=0.009$) after EPO. Resting $\dot{V}O_2$ decreased from 8.48 \pm 1.93 to 6.76 \pm 1.30 ml/min/kg, $p=0.001$ and peak exercise $\dot{V}O_2$ decreased from 26.69 \pm 5.04 to 23.80 \pm 3.51, $p=0.07$. Correcting anemia in ESRD had no short term effects on 2D echo indices of cardiac performance, however, resting hemodynamics (CI & $\dot{V}O_2$) and exercise tolerance improved. Further changes in cardiac performance may occur in long term follow-up.

16

PERCUTANEOUS TRANSEPTAL DOUBLE BALLOON VALVULOPLASTY FOR CONGENITAL MITRAL STENOSIS

Ronald G. Grifka, MD*, Michael R. Nihill, MD, FAAP, Charles E. Mullins, MD, FAAP, Texas Children's Hospital, Houston, Texas

Since surgical treatment of congenital mitral stenosis (CMS) is not always successful, we have undertaken to perform balloon valvuloplasty on pts with CMS. We reviewed our results of percutaneous transseptal double BV for CMS. Eight pts underwent a total of 10 procedures. All had symptoms of severe MS. Two had isolated CMS, 6 had additional cardiac defects; 1 had previous surgical valvotomy. Ages ranged from 7 mos-36 yrs (md 9 yrs), weights 4.5-84 kg (md 20 kg). 5/10 were heparinized. The balloon:annulus ratio was 0.85-1.17. All procedures were well tolerated.

Post-BV, all had marked clinical improvement. There was no significant change in LVEDP, and the "a" wave to LVEDP gradient was reduced from 25.1 to 9.6 mmHg ($p < 0.001$). Complications included 1 hemopericardium evacuated in the cath lab, 1 (Shone complex) developed 2+ mitral regurgitation (MR), 2 developed trivial MR, 1/5 not heparinized had a transient ischemic attack. Two had repeat BV after 7 mos due to restenosis: one subsequently expired after surgical valvotomy. Follow-up on 6 pts (mean 24 mos) reveals no recurrence of symptoms or increased MR. CONCLUSIONS: 1) Percutaneous transseptal double BV is effective and safe for reducing the valvular gradient in many forms of CMS. 2) Significant MR is uncommon post-BV. 3) Transseptal technique allows LA and LV pressure monitoring to assess the BV results in the cath lab. 4) Heparin administration is recommended after transseptal access to the LA.

17

A PROSPECTIVE RANDOMIZED STUDY COMPARING SURGICAL AND BALLOON ANGIOPLASTY TREATMENT OF NATIVE COARCTATION Robert E. Shaddy FAAP*, Jane E. Sturtevant, Herbert D. Ruttenberg FAAP, Richard B. Jaffe, Edwin C. McGough, Mark M. Boucek FAAP. Primary Children's Medical Center, Salt Lake City, Utah

From 1985 to 1988, we prospectively randomized 27 pts (age 3-10 yrs) with native coarctation of the aorta (COA) to receive either balloon coarctation angioplasty (BCA) (n=14) or surgical end-to-end anastomosis (SURG) (n=13). Our purpose was to prospectively compare the results, complications, and incidence of aneurysms in these two groups. The groups were similar in age (5.8 vs 5.8 yrs, BCA vs SURG), and pre-treatment peak systolic pressure gradient across the COA (46 vs 51 mm Hg). After treatment, residual pressure gradient was similar by both catheterization performed 14 \pm 6 months later (11 \pm 11 vs 8 \pm 6 mm Hg, n=14), and by blood pressure cuff measured 19 \pm 11 months later (12 \pm 14 vs 7 \pm 8 mm Hg). Complications were not significantly different between groups: BCA - one pt severe hyper-tension; SURG - one pt vocal cord paralysis, one pt lower extremity weakness and one pt post-operative bleeding. MRI (n=14) and angiography (n=14) were performed at 17 \pm 2 months after treatment in 24 pts. Aneurysms developed in 4 pts after BCA and 1 pt after SURG. We conclude that in this small group of randomized pts there is no significant difference in the results or complications between pts with COA treated with BCA or SURG. BCA tends to result in more aneurysms than SURG.

18

TRANSCATHETER CLOSURE OF SECUNDUM ASD IN PEDIATRIC PATIENTS: THE FIRST YEAR'S EXPERIENCE. Nancy D. Bridges, MD*, Jane W.

Newburger MD, John E. Mayer MD, and James E. Lock MD. Cardiology Department, The Children's Hospital, Boston.

Clinical trials of the "Clamshell" Occluder (Bard, USCI), an umbrella used for catheter closure of secundum ASDs (ASD2) <22 mm in diameter, began in 2/89. We retrospectively reviewed and compared all pediatric patients (pts) having transcatheter or surgical closure of ASD2 at Children's Hospital, Boston, in 1989. Results were (mean, range):

	# of pts	age (yrs)	days in ICU	days in ward	days on blood given
surg	21	6.2(1.1-17.7)	1(1-2)	5(4-5)	11/21
cath	23	6.6(1.8-17.7)	0	2(2)	0

There were no deaths in either group; by physical examination, all had closure of the ASD. In the transcatheter group, fluoroscopy time was 37 (20-51) minutes; 2 pts also had balloon dilation of the pulmonary valve. There were no catheterization complications. Residual atrial leaks (small or moderate) were seen by color Doppler in 3 pts. Hospital charges averaged \$6,427. In the surgical group, pump time averaged 34 (20-76) minutes. Complications included ectopic atrial tachycardia (1), pneumothorax (2), minor GI bleeding (1), and post-extubation stridor treated with steroids (1). Echo assessment of defect closure was not performed in surgical pts. Hospital charges averaged \$15,759.

In summary: Both procedures were safe and effective. The 2 groups may not be entirely comparable. Transcatheter closure appears to result in less ICU care, shorter hospitalization, fewer blood transfusions, and lower hospital charges than surgical closure. Transcatheter closure may be an acceptable alternative to surgical closure for anatomically suitable ASD2.

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EXERCISE RESPONSE OF PATIENTS WITH AORTIC STENOSIS: REPORT OF THE SECOND NATURAL HISTORY STUDY (NHS-2).

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Exercise capacity is an important measure of disease severity. We report the results of treadmill exercise testing of 134 pts. with AS participating in NHS-2. The 108 M and 26 F ranged from 19-49 (median=31.5) yrs. old. Thirty-three had no prior operation; 63 had aortic valvotomy and 38 had aortic valve replacement (AVR). A max effort during exercise was achieved by 111. The test was terminated by the examiner in five instances (arrhythmia-1; syncope-1; leg fatigue-1; and ST segment Δ and/or abnormal Bp-2). Exercise duration (% pred.) was 86.8% which is ($P<0.05$) less than normal. Higher Quetelet index, wt. and NYHA class were negatively associated ($P<0.05$) with exercise duration. Prior valvotomy or AVR were negatively associated with $\dot{V}O_{2max}$. HR max was 95.1% of pred. which is ($P<0.05$) less than normal. HR max was lower for pts. who had AVR than valvotomy or medical treatment. The occurrence of multiform PVCs, couplets and VT were influenced ($P<0.05$) by clinical status, prior aortic valvotomy or AVR and M gender. There was a positive correlation between aortic gradient (Doppler) and ST segment Δ . Aerobic capacity and HR max are reduced in pts. with AS. AS severity and management affect aerobic capacity, the presence of arrhythmia and degree of ST segment Δ .

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LONG TERM RESULTS OF SEVERE AORTIC VALVE STENOSIS IN INFANCY

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Long term morbidity and mortality were evaluated in the survivors of 51 consecutive infants with severe aortic valve stenosis treated surgically in the first 10 weeks of life from 1957 to 1987. There were 30 perioperative deaths (58.8%). The 21 early survivors (those who were discharged from the hospital) have been followed from 3 to 27 years (yrs)(median 8.5). The 10 yr actuarial survival is 100%. There have been 2 late deaths, 1 suddenly at age 13 yrs, and the other at age 14 yrs following dislodgement of a prosthetic valve. Freedom from reoperation at 10 yrs is 90.4%. Six patients have required reoperation: 3 underwent repeat valvotomies for persistent stenosis 2 to 15 yrs after the initial operation and 4 have had valve replacements for progressing severity of aortic insufficiency (AI) 14 to 27 yrs after the initial operation. One of these had required a repeat valvotomy at age 15 yrs. The 15 remaining patients have Doppler predicted residual gradients from 20 to 64 mmHg (mean 45mmHg); 12 have mild or no AI, 2 have moderate AI and 1 has moderately severe AI. In conclusion, survivors of surgically treated aortic valve stenosis in infancy have a relatively good long term prognosis and a high freedom from reoperation before adolescence.

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RESULTS AND LONG TERM FOLLOW UP OF PATIENTS WITH MECHANICAL PROSTHETIC VALVES

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Although valve replacement (repl) is commonplace in pediatrics there are few reported long-term evaluations of large numbers of pts from a single institution. Between 1971 & 1990, 108 pts (median age 11.5 yrs) underwent 125 valve repl (Bjork Shiley 77, St Jude 41, Omni-Science 6, Medtronic Hall 1) for regurgitation (51), stenosis (39) or both (18). There were 10 operative (op) and 6 late deaths (1.5 - 7 yrs post-op). Major complications included bleeding (6), stroke (3), embolism (2), pannus formation (5), endocarditis (4), perivalvular leak (4) & heart block (6). Follow-up evaluation (median 7 yrs) of 74 of 92 pts revealed 68 to be in NYHA I, & 6 to be in class II.

	(n)	%	%	%	% Overall
	<u>Pts</u>	<u>Mort.</u>	<u>Morb.</u>	<u>Re-op</u>	<u>Survival</u>
AV	72	8.4	15	12.6	92
MV	29	27.5	9.5	9.5	72
AV + MV	3	66.6	0	0	33
TV/PV	<u>4</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>100</u>
Total	108	15	11	10	85

High op mortality with MV and MV + AV repl correlated with severity of the defect.

Conclusions: Despite 9% op mortality and 18% incidence of complications, overall prognosis appears to be good. Late sudden deaths (6%) warrant close long-term follow-up especially with AV repl.

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AORTIC VALVE REPLACEMENT IN CHILDREN: LONG-TERM FOLLOW-UP.*Douglas S. Moodie, M.D. FAAP, Usama A. Hanhan, M.D., Richard Sterba, M.D. FAAP, Eliot Rosenkranz, M.D., Andrea Homa, BS Pediatric Cardiology, Cleveland Clinic

Few studies have dealt with the long-term follow-up (FU) of children with aortic valve replacement (AVR). Thirty-four children underwent AVR from 1972-1988, 28 (82%) males and 6 (18%) females, mean age 17 years (yrs), range 10-20 yrs. The most common symptoms were fatigue (69%), shortness of breath (67%) and dyspnea on exertion (57%). Seven patients (pts) (21%) were FC III or IV and the remaining number of pts were FC I and II. Thirty-three pts (97%) had a systolic murmur, 29 pts (88%) a diastolic murmur, 23 pts (74%) left ventricular hypertrophy and 24 pts (71%) cardiomegaly. Twenty-two pts underwent isolated AVR; 12 pts had additional procedures. Thirty-six valves were implanted: 17 (46%) St. Jude, 5 (14%) Bjork Shiley, and 3 (8%) Carpentier Edwards. Seven pts (20%) had tissue valve prosthesis. There was 1 hospital death (2.9%). FU was obtained on 30 of 33 pts (91%) with a mean FU of 80 mos. Ages of pts at time of FU ranged from 15-35 yrs, mean 24 yrs. One pt (3%) had a major thromboembolic event and 1 pt (3%) had prosthetic valve endocarditis. Five pts (16%) required reoperation. There were 3 late deaths. Actuarial survival curves showed 96% survival at 5 yrs, 84% at 10 yrs. Twenty-three of 27 (85%) survivors are NYHA FC I at the time of FU. AVR in children can be performed with low mortality and morbidity and excellent long term results.

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CONGENITAL HEART DEFECTS IN THE SECOND GENERATION - A COMPARATIVE STUDY
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A 25 year prospective study of pregnancy in 236 mothers with congenital heart defects (CHD) with a 3 year follow-up of their infants, was compared with a study of 119 affected fathers and their 419 children. These probands had been patients in the same cardiac clinic under the author, most originally seen prior to 1960. Results were grouped according to the parental diagnosis in seven major categories. CHD was present in 55 (13.2%) of the mothers' children and 62 (14.8%) of the fathers' children, not significantly different. Concordance, however, was 53% in the maternal study, 32% in the paternal study, ($P=0.025$). There was significant dominance in maternal group with ventricular septal defect and in the paternal group of pulmonic stenosis.

Over the 25+ years of this study, several smaller studies indicated children of affected mothers were more likely to have CHD than those of fathers. Several studies had the same range as above. A compilation of ten outstanding studies identifies 3912 probands with 8080 progeny, 375 of whom were affected. Most of these studies were not prospective. The overall incidence of CHD in these children was 4% (148 of 3721) in the male probands, 5% (218 of 4321) in the female probands, ($P=0.05$). The incidence of CHD in the offspring of affected parents is higher than originally suspected with a possible slight dominance in the progeny of maternal probands.

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VENTRICULAR SEPTAL DEFECT IN INFANTS: AN EIGHT-YEAR POPULATION-BASED STUDY. Charlotte Ferencz, MD, FAAP,* Catherine A. Neill, MD, FAAP, Joel I. Brenner, MD, FAAP, Lowell W. Perry, MD, FAAP, Gerard R. Martin, MD, FAAP, and the Baltimore-Washington Infant Study Group. Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, Maryland.

A regional collaborative case-control study ascertained 3583 infants with cardiovascular malformations (CVM) between 1981 and 1988. Ventricular septal defect (VSD) increased in live-birth prevalence from 9/10,000 in 1981-82 to 20/10,000 in 1987-88. The ratio of membranous defects (VSDme; N=869) to muscular defects (VSDmu; N=307) decreased from 10:1 in 1981-82 to 2:1 in 1987-88. Diagnosis by echocardiography alone increased from 60% in 1981-82 to 95% in 1987-88. Of 533 VSDme and 133 VSDmu (1981-86), 14% in each group closed by one year. Noncardiac anomalies (NCA) were present in 98 (18%) VSDme and 10 (8%) VSDmu. Atrial septal defect or patent ductus arteriosus occurred in 47% of VSDme with NCA and in only 13% of isolated VSDme. Multivariate analyses of case-control differences revealed no risk factors for VSDmu. Suspect risk factors for isolated VSDme included: familial CVM (odds ratio [OR]=4.52, 99% confidence interval [CI]: 1.80, 11.13), diabetes (OR=4.60, CI: 1.26, 16.60), pesticides (OR=1.51, CI: 1.10, 2.07), and working under hot temperatures (OR=11.04, CI: 1.33, 90.92). VSDme identified as small or closed (N=48) did not differ from larger defects in risk factor profile. NHLBI R37 HL25629.

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POSTOPERATIVE VENTRICULAR SEPTAL DEFECT. 30-35 YEAR FOLLOW-UP OF 289 PATIENTS. James H. Moller, FAAP*, Ceeya Patton, Richard L. Varco, and C. Walton Lillehei. Department of Pediatrics, University of Minnesota

This study was designed to determine the clinical status, causes of death, and effects of pulmonary vascular disease and of conduction abnormalities during a postoperative period of 30-35 years in 296 consecutive survivors of closure of ventricular septal defect. Of the 296 survivors, current status was determined in 289 patients, with 7 (2%) being lost to follow-up. 7,912 years of follow-up are included. Death occurred in 59 (20%) of the survivors, with higher mortality rates in those operated after the age of 2 years, those with pulmonary resistance > 7 mmHg/L/min/M2 (51%), and those with complete heart block (78%). Of 37 patients with transient heart block postoperatively, 8 (22%) have died, 3 from pulmonary vascular disease, 2 suddenly, 2 from unknown causes, and 1 from complete heart block. Twenty other patients had a postoperative dysrhythmia and none died. Nine episodes of infective endocarditis occurred (11.4/10,000 years). Nine of 296 offspring (3%) have a cardiac malformation. Most patients are in NYHA class I. The data show good results for these patients operated upon during an early era (1954-1960), and support the current trend to operate on patients during infancy and with low pulmonary vascular resistance. The data should be useful to cardiologists providing care to adults who underwent cardiac surgery during childhood.

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Esophageal Recording and Pacing - An Adjunct In the Management of Pediatric Arrhythmias

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Since August of 1987, we have performed 356 esophageal recording and pacing studies for a variety of disorders in 290 patients between the ages of 1 hour and 36 years. Studies were performed for a) evaluation of manifest W-P-W (n = 89), b) supraventricular tachycardia not related to W-P-W (n = 133), c) conversion of atrial reentrant tachycardia (i.e. - flutter, n=76), d) ventricular tachycardia (n=2), e) evaluation of palpitations (n=29), f) evaluation of suspected neurally-mediated syncope (n=9), and g) assessment of SA or AV node function (n=20). A bipolar pill electrode (patients 6 years of age and older) or a bipolar silastic coronary sinus pacing catheter was used for recording and stimulating.

These studies resulted in 1) establishing a presumptive tachycardia mechanism in 102 patients without W-P-W, based on VA interval and A:V ratio during tachycardia, and response to pacing, 2) successful conversion to sinus rhythm in 38/38 patients presenting with new AV reentrant tachycardias (including one pair of thoraco-abdominal Siamese twins), 3) successful conversion of 63/76 cases of atrial flutter (83%), and 4) establishing a diagnosis in 16/29 patients with palpitations. In addition, tachycardia inducibility was used to assess acute drug therapy in 86 studies, and chronic therapy in 66 f/u studies. Esophageal pacing was also used successfully to establish AV synchrony in 9 patients with post-operative junctional ectopic tachycardia for up to 72 hours. Studies were abandoned due to lack of cooperation in only 3 patients, and there was no significant morbidity from any aspects of the procedures.

We conclude that esophageal recording and pacing techniques offer a safe and extremely effective adjunct to the diagnosis and therapy of most pediatric arrhythmias.

CARDIOVASCULAR ABNORMALITIES IN INFANTS PRENATALLY-EXPOSED TO COCAINE. Joseph J. Frassica, MD*, E. John Orav, PhD, Tracie L. Miller, MD, Steven E. Lipshultz, MD FAAP, Boston City, Children's, and Franciscan Children's Hospitals, Boston, MA.

Cocaine abuse during pregnancy is a growing public health issue in the United States. However, little information exists on the specific effects of cocaine upon pregnancy and the developing fetus. This retrospective study examines the relationship between maternal cocaine use during pregnancy and the occurrence of congenital cardiovascular abnormalities.

All neonatal drug screens performed at Boston City Hospital over an 18 month period were reviewed (n=554); 39% (n=214) of screened high risk neonates had toxicologic screens positive for cocaine and 61% (n=340) of neonates were negative for cocaine. Our goal was to compare the occurrence of cardiovascular malformations and electrocardiographic abnormalities between these 2 groups, and to the general population rates reported in the literature. Matches were sought between these 554 infants and our pediatric cardiology data base, which consisted of inpatient consultation, outpatient consultation and electrocardiographic testing. Forty-nine patients had drug screens and were also entered in our cardiology data base: 25 had both consultations and electrocardiograms, and 24 had electrocardiograms only. The frequency of congenital cardiovascular malformations in the cocaine positive population was significantly higher ($p < .001$) than the general population (65/1000 vs. 8.6/1000). In addition, the frequency of cardiac anomalies among our group of cocaine-positive children was significantly higher ($p = .024$) than the frequency of these anomalies among the cocaine-negative comparison group (65/1000 vs 18/1000). A variety of electrocardiographic abnormalities, high-grade ventricular ectopy and respiratory arrests were also noted in our study population.

Cocaine exposure during prenatal life appears to predispose infants to structural cardiovascular malformations, electrocardiographic abnormalities and possibly cardiopulmonary autonomic dysfunction.

ELEVATED SERUM LIDOCAINE LEVELS DURING CARDIAC CATHETERIZATION IN CHILDREN

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In a prospective examination of 10 patients (PTS) aged 8 months to 16 yrs (median age = 39 mo), serum lidocaine (LIDO) levels were obtained during cardiac catheterization. Six PTS had a body surface area $\leq 1 \text{ m}^2$ (mean wgt = 10.3 kg, range 6.45 - 15 kg) and 4 PTS had a body surface area $> 1 \text{ m}^2$ (mean wgt = 52.7 kg, range 40.2 - 64 kg). Prior to percutaneous catheter insertion, LIDO was subcutaneously infiltrated into the femoral triangle. Frequent aspirations were performed to avoid inadvertent intravascular infiltration. In 7 PTS, several sites or additional infiltrations of LIDO were necessary before line placement was accomplished. Serum LIDO levels using the FPIA technique were obtained 25 - 120 min, (mean = 95 min) following infiltration. The anti-arrhythmic therapeutic range is 2 - 5 mcg/ml. The amount of LIDO administered to all PTS was 2 - 47 mg/kg. The mean LIDO administered to PTS with a body surface area $\leq 1 \text{ m}^2$ was 20.4 mg/kg and to PTS with a body surface area $> 1 \text{ m}^2$ was 3.55 mg/kg. In the 6 PTS with a BSA $\leq 1 \text{ m}^2$, 2 PTS had toxic levels of LIDO (7.2 mcg/ml and 6.8 mcg/ml), 3 had therapeutic levels (3.3 mcg/ml, 3.2 mcg/ml, and 2.4 mcg/ml), and 1 had a level of 1 mcg/ml. Of the 4 PTS with a BSA $> 1 \text{ m}^2$, all LIDO levels were ≤ 1.0 mcg/ml. Although no PTS experienced any serious untoward effects, the two PTS with toxic LIDO levels were noted to be neurologically depressed following cardiac catheterization.

Appreciation that toxic serum LIDO levels may occur in pediatric PTS during routine infiltration is necessary. Since children $\leq 1 \text{ m}^2$ (15kg) appear to be at increased risk for LIDO toxicity, the 0.5% solution of LIDO should be used in these PTS. The monitoring of LIDO is especially important when electrophysiologic data is obtained since increased LIDO levels may lead to suppression of the arrhythmia.

PHASE IMAGE ANALYSIS OF ABNORMAL SITES OF VENTRICULAR ACTIVATION IN YOUNG PATIENTS: OPERATIVE VALIDATION AND CORRELATION WITH CATHETER ENDOCARDIAL MAPPING.

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We prospectively investigated the accuracy of phase analysis (PA) of scintigraphic imaging in predicting the site of onset of ventricular activation in young pts with electrophysiologic (EP) disorders. 19 pts (mean age 12 yrs) with preexcitation (n=15) or ventricular tachycardia (VT) (n=4) were studied independently by PA and EP methods. Of the 8 pts with congenital heart disease, 4 had Ebstein's anomaly. Accessory AV connections (AC) were localized to a 10 site grid based on the AV annulus. The site of the earliest phase angle in any of 3 scintigraphic views during preexcited sinus rhythm or VT was compared to catheter localization of retrograde atrial activation during reciprocating tachycardia or ventricular activation during VT. 10 pts had subsequent epicardial operative mapping.

The PA localization of 11 free wall pathways (7 right) (4 left) and 1 Mahaim fiber was concordant with EP study. The resolution of 2/3 septal or paraseptal pathways was inconclusive. PA localization of ventricular activation was consistent with EP mapping in 3/4 pts with VT. Operative epicardial mapping confirmed the EP predicted sites in 10/10 pts (8AC, 2VT).

Conc: 1) Free wall AC and sites of VT may be accurately defined by PA of scintigraphic imaging; 2) regional dyssynergy, eg Ebstein's anomaly, does not preclude accurate PA; and 3) pt age/size are not limiting factors for this technique. PA provides data complementary to catheter endocardial mapping and may enhance preoperative localization of ACs and VT foci.

SURGICAL CLOSURE OF THE TRICUSPID VALVE FOR PULMONARY ATRESIA WITH INTACT VENTRICULAR SEPTUM AND LARGE RV-CORONARY ARTERY SINUSOIDS.

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In pulmonary atresia with intact ventricular septum (PAcIVS) and large RV-coronary artery connections (sinusoids), decompression of the RV poses a risk of coronary steal and therefore ischemia. In 5 patients with PAcIVS and sinusoids, the tricuspid valve (TV) was closed surgically. Four had a concurrent atrial septectomy and shunt (systemic-pulmonary in 3 neonates and cavo-pulmonary in 1 infant). Four survived. Before TV closure, three had ST/T wave ECG changes suggestive of ischemia; these resolved after surgery. Angiography after TV closure showed no RV filling and normal coronary arteries. Echocardiography showed a residual RV cavity without significant change in volume over 3-4 years' follow-up. Two have had a Fontan operation with one death from dysrhythmia. Two are well after cavo-pulmonary shunt. We believe that the optimal approach for patients with PAcIVS and sinusoids is: a) neonatal cardiac cath for evaluation of sinusoids and balloon septostomy, followed by b) a 4 mm Goretex systemic-pulmonary shunt, c) repeat cardiac cath at 4-6 months of age and if sinusoids still large, d) TV closure with cavo-pulmonary shunt; e) modified Fontan operation at 2-4 years of age.

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EARLY MODIFIED FONTAN OPERATION IN CHILDREN < 2 YEARS OF AGE. Howard Weber* FAAP, John Myers, John Waldhausen, Marie Gleason FAAP, Steve Cyran FAAP, & Barry Baylen FAAP. Department of Pediatrics & Surgery, Milton S Hershey Medical Center, Pennsylvania State University.

The Fontan operation and its modifications (MFO) remain the final definitive procedure for many patients (pts) with complex congenital heart disease. Many series report age <4 years a risk factor for increased mortality. Successful outcome in children < 2 yrs is rare. We have performed the MFO in 12 consecutive pts < 2 yrs of age (mean 18 months, range 7-24 months) with no early mortality. Preoperative anatomy was tricuspid atresia (2), left heart hypoplasia (4), single ventricle (4) & complex DORV (2). Nine of 12 (75%) required a palliative shunt prior to MFO. All pts had sinus rhythm preoperatively. Eight (67%) developed immediate postoperative (postop) arrhythmias (supraventricular tachycardia (3), junctional rhythm (5)). Mean duration of hospitalization was 23 days (range 11-43 days). Postop recurrent pleural effusions occurred in 7 (58%). There was 1 late death (8%) 6 months postop in a pt who suffered severe neurologic injury at surgery. The 11 survivors (mean followup 9 months, range 5-17 months) are all NYHA Functional Class I. One has a mild neurologic deficit. Only 2 pts (17%) have late postop arrhythmias (junctional rhythm (1), supraventricular tachycardia/junctional rhythm (1)). None require pacemaker therapy. Thus age < 2 yrs was not a risk factor for increased mortality or morbidity. Earlier MFO avoids chronic hypoxemia & ventricular volume overload associated with multiple/chronic shunt palliation. Consequently we advocate MFO at < 2 yrs which may preserve ventricular function and provide a superior result.

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RIGHT VENTRICULAR HYPERTROPHY MANY YEARS AFTER SURGERY FOR COARCTATION OF THE AORTA, DIAGNOSED WITH ELECTROCARDIOGRAPHIC BODY SURFACE POTENTIAL MAPPING. JEROME LIEBMAN FAAP, CECIL THOMAS, RENNIE FRAENKEL, GIORA BEN-SHACHAR FAAP, YORAM RUDY, CASE WESTERN RESERVE UNIVERSITY, SCHOOL OF MEDICINE, CLEVELAND, OHIO

Patients with coarctation of the aorta who had had surgery in the remote past are often diagnosed on standard ECG as having partial RBBB. Twenty-two patients had body surface potential mapping (BSPM) with a 180 electrode system, of whom 5 had additional aortic stenosis and none had ever had intracardiac communication. The average age of the BSPM was 13.5 years and average of the initial surgery for coarctation was 4.2 years. In ten of the 22 cases, congestive heart failure had been present in infancy. Cardiac catheterization was performed near the time of the BSPM in 11 and only one, (40mmHg), had elevation of right ventricular pressure. Every case had evidence for epicardial right ventricular breakthrough on the BSPM, a finding believed to indicate right ventricular activation from endocardium to epicardium via the normal Purkinje system, so that RBBB was not present. RVH with terminal right conduction delay was present in 17 (9 with additional LVH) and LVH was present in 5. RVH could be considered with standard ECG in 7, and Frank system VCG in only 11 of the 17. The reason for the persistent electrocardiographic RVH may be right ventricular hyperplasia in utero which never disappears.

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OXYGEN DERIVED FREE RADICALS MODULATE PULMONARY VASOMOTION IN VITRO.

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Hyperoxia may alter pulmonary arterial pressure profoundly. To determine if oxygen-derived free radicals modulate pulmonary vasomotion, isolated rings of small porcine pulmonary artery were placed in organ chambers filled with physiologic buffer and exposed to increasing concentrations of oxygen derived free radicals generated by xanthine and xanthine oxidase. At basal tension, oxygen-derived free radicals caused small concentration-dependent endothelium-independent contractions which were prevented by superoxide dismutase (SOD), SOD plus catalase, SOD plus dimethylsulfoxide (DMSO), and indomethacin; superoxide anion is implicated as the effector. In rings contracted with histamine, oxygen-derived free radicals caused endothelium-dependent relaxations under control conditions and in the presence of SOD. No change in tension was observed in the presence of SOD plus catalase or SOD plus DMSO, implicating hydrogen peroxide as the agonist causing relaxation. Rings with endothelium relaxed to acetylcholine following exposure to oxygen derived free radicals indicating an intact endothelial layer. These data suggest that oxygen derived free radicals can cause both contraction and relaxation, and may, in part, explain the changes in pulmonary vasomotion to hyperoxia.

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RAPID, NEAR TOTAL "FADE" OF THE CHRONOTROPIC RESPONSE DURING VAGAL STIMULATION IN THE NEWBORN CANINE - EVIDENCE FOR A PROMINENT NEUROPEPTIDE - Y EFFECT. Shiyou Yamasaki, Adrienne Stolfi, Madeleen S. Mas, Lawrence S. Fox, Arthur S. Pickoff* Tulane University School of Medicine, Department of Pediatrics, New Orleans, Louisiana

Prompted by an inability to maintain stable responses to vagal stimulation (VS) in the newborn, we evaluated the time-dependent changes in sinus cycle length (SCL) in 7 anesthetized newborn canines, ages 4-10 days, during 30 second trains of VS (8 Hz), delivered every 2 minutes to the right cervical vago-sympathetic trunk (a nerve with predominantly parasympathetic and some sympathetic fibers). The first 30 second train prolonged SCL by $58 \pm 35\%$, but during subsequent trains the response faded (99% attenuation after only 6.4 ± 1.7 trains). Recovery of the chronotropic response was complete by 40 minutes after cessation of VS. Post-receptor desensitization was excluded as a mechanism of fade by demonstrating a preserved response to exogenous acetylcholine (50-100 ug/kg IV). Neuropeptide-Y, a non-adrenergic sympathetic co-transmitter with known autonomic inhibitory effects, was administered (50 ug/kg IV) to 6 other neonates and resulted in an immediate loss of response to VS with a time course of recovery similar to that observed for fade caused by VS. Furthermore, in 6 chemically sympathectomized newborns (6-OH dopamine, 50 mg/kg IP x 3 days, tyramine verified) stable chronotropic responses were observed during VS without fade. We conclude that 1) Neuropeptide-Y is a potent inhibitor of cardiac vagal responses in the neonate, and 2) Even low levels of sympathetic activity may profoundly attenuate parasympathetic modulation of cardiac physiology in the newborn.

METABOLIC CORRELATES OF FUNCTION AND ADENOSINE PRODUCTION IN THE IMMATURE AND MATURE RABBIT HEART.

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The links between metabolism and myocardial adenosine (ADO) production and function in the developing heart were studied with graded ischemia in isolated immature (IM) and mature (M) rabbit hearts. Isovolumic hearts were perfused at rates of 8, 6, 4, 2, and 1 ml/min/g. ^{31}P NMR spectroscopy was used to measure changes in the phosphorylation potential (CrP/Pi). Coronary effluent was collected to measure ADO concentration. Coronary vascular resistance (R), the first derivative of left ventricular pressure (dP/dt) and double product (HR*LVP) were also measured.

Results: R, dP/dt, double product, ADO levels, and CrP/Pi were all lower in IM under basal conditions. Graded reductions in flow caused similar decreases in dP/dt and double product in IM and M but R was decreased more in IM at all reductions in flow. ADO levels increased with reductions in flow in both IM and M and correlated with both R and CrP/Pi. Myocardial function (dP/dt and double product) correlated well with CrP/Pi in M but only the lowest levels of function were associated with lower CrP/Pi in IM.

Conclusion: ADO production appears to be related to CrP/Pi in both IM and M hearts. Changes in CrP/Pi correlated with function in M but not IM suggesting developmental differences in the link between metabolism and function in IM and M hearts.

cAMP-MEDIATED CARDIOMYOCYTE HYPERTROPHY REQUIRES EXCITATION-CONTRACTION COUPLING.

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Agents which activate adenylate cyclase, such as β agonists and forskolin (Fk), have recently been shown to cause protein accumulation in cultured ventricular myocytes. However, cell tension is also a powerful hypertrophic stimulus. We hypothesized that cAMP-mediated hypertrophy could be explained by increased cell tension during contractions because of the inotropic effect of cAMP. To separate contraction-dependent from contraction-independent effects of cAMP, newborn rat ventricular myocyte cultures were treated with 10^{-6} M Fk, with 10^{-6} M nifedipine (Nf), with both drugs (Fk+Nf), or with drug vehicle alone (controls). All culture media included 15% horse serum, which induces cells to contract spontaneously. Spontaneous contractions, common in control and Fk cultures, were >90% suppressed in Nf and Fk+Nf cultures. By video motion analysis, contraction amplitude in Fk cultures was $171 \pm 18\%$ (SEM) of controls ($p < 0.05$). After 48 hours of drug exposure, cells were harvested from culture dishes by brief trypsin exposure, washed with protein-free buffer by repeated centrifugation, and counted by hemacytometer. Protein was measured by dye-binding assay. Cell protein content was significantly higher in Fk cultures than control (792 ± 169 vs. 508 ± 85 pg/cell, $p < 0.05$), but in the presence of Nf, Fk had no effect (Fk+Nf 574 ± 93 vs. Nf 575 ± 123 pg/cell). We conclude that the positive inotropic effect of cAMP results in cell hypertrophy by increasing cell tension, because suppressing contraction with Nf eliminated the hypertrophic effect of Fk.

MECHANICAL FUNCTION AND FATTY ACID OXIDATION IN THE NEONATAL PIG HEART SUBJECTED TO HYPOXIA AND REOXYGENATION.

Robert J. Ascuitto*, Nancy T. Ross-Ascuitto, David Ramage, Kathleen H. McDonough.

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Fatty acids (FA) have been implicated in hypoxic myocardial injury. However, there are no studies on FA utilization by neonatal hearts, during hypoxia or reoxygenation. We studied isolated, isovolumically-beating piglet hearts (N=8), 12hr to 2d of age, perfused with an erythrocyte-enriched buffer (Hct~15%), containing glucose, lactate and palmitate. Each heart was perfused (60 mmHg) during three consecutive 30min periods: control, [O₂]=7.7vol%; hypoxia, [O₂]=0.6 vol% (10% Hb Sat) and reoxygenation. Left ventricular peak systolic pressure (PSP), end diastolic pressure (EDP), coronary flow (CF), myocardial O₂ consumption (MVO₂) and FA oxidation (FAOx) were measured. FAOx was determined by ^{14}C release from ^{14}C -palmitate. Early in hypoxia, CF increased 3-4 fold but then decreased. During hypoxia, hearts released lactate and, despite mechanical failure (PSP~56mmHg and EDP~17mmHg), continued to oxidize FA (50% of MVO₂). After 30 min. of reoxygenation (RE-OX), PSP was depressed, EDP elevated and MVO₂ was similar to control. However, FAOx was 120% above control. Thus, neonatal pig hearts exhibit mechanical failure, yet continue to oxidize FA during severe hypoxia. Moreover, despite depressed mechanical function and reduced MVO₂, FAOx was enhanced post-hypoxia. Theoretically, the enhanced FAOx may result in inefficient O₂ use when ATP is being restored.

	CONTROL	END-HYPOX	RE-OX
PSP mmHg	102.5±2.5	56.4±2.8	81.3±2.7
EDP mmHg	1.6±0.2	17.1±2.1	5.6±1.7
CF ml/min/g	3.3±0.1	4.8±0.8	2.6±0.3
MVO ₂ ul/min/g	60.1±1.5	21.7±2.3	52.0±0.7
FAOx nmol/min/g	33.8±1.3	22.8±3.7	74.2±2.6

CHRONIC HYPOXIA INCREASES CORONARY VASODILATOR CAPACITY OF DEVELOPING RABBITS

Gerard Holmes* and Michael L. Epstein FAAP
Dept. of Pediatrics, University of Florida

We have previously demonstrated increased maximum coronary vasodilator response to adenosine in young rabbits raised in hypoxia. To further test the effect of early development in hypoxia on capacity for coronary perfusion, coronary vasodilator response to two additional stimuli, 90 sec. flow occlusion (R) and nitroprusside (N), were studied in isolated, unloaded, constant pressure perfused hearts of hypoxic (HX) (raised in PO₂=60 Torr from age 3 days) and normoxic (NX) rabbits at age 5 weeks. Regional flow at maximum vasodilation due to N was measured using microspheres. HX rabbits developed moderate RVH and elevated hematocrit but not LVH or heart failure. Values (Mean±SEM) for peak flow responses are as follows:

group	R (n)		N (n)	
	ml/min/g		ml/min/g	
	Total	Total	RV	LV
NX	11.8(6)	10.2(9)	10.5(9)	10.7(9)
	±1.4	±0.5	±0.9	±0.4
HX	15.7(10)*	12.6(8)*	14.4(8)*	14.6(8)*
	±1.2	±1.2	±1.5	±1.5

(*increased from NX -Student's T Test, $p < .05$)
These results show that maximum vasodilator responses to R and N are also increased in HX rabbits. Increased maximum vasodilator response to three different stimuli suggests morphologic alteration in the coronary vascular bed rather than changes in receptors. Thus, morphologic vascular alteration may be important to adaptation of developing animals to moderate hypoxia by improving coronary perfusion capacity.

Pericardial Constrictive Tissue Buffers Cardiac Transmural Pressures

Meyer et al¹ present a fascinating investigation of the much disputed Kussmaul's sign² in patients with constrictive pericarditis. They observed that during ordinary breathing, as opposed to deep inspiration, the atrial pressures do not seem to vary much in constriction. Indeed, a review of some of my own catheterization traces supports this. At bedside the neck veins may appear *not to collapse normally* rather than to distend, at least during ordinary breathing. In any case, pressure studies in the jugular veins in such patients would be of considerable interest for clinical diagnosis as well as for hemodynamic comparison with atrial physiology.

I also wish to support the authors' hypothesis that during inspiration the effect of increased transmural pressure on left ventricular systolic wall stress (afterload) "may theoretically be attenuated" by the increased wall thickness due to the inflammatory process and scar tissue. In constrictive pericarditis we reported a normal control level of atrial natriuretic peptide (ANP) despite marked atrial hypertension; the ANP level markedly increased immediately after pericardiectomy.³ This indicates that attenuation of transmural pressure changes by constricting tissue is more than theoretic. (The significance of transmural pressure,⁴ accounting for atrial stretch, is equally supported by reports of a comparable ANP increase immediately upon drainage of tamponading pericardial effusion; of course, Kussmaul's sign is not seen in tamponade.²) Meyer et al¹ make significant contributions to our understanding of this fascinating phenomenon. It should lead to further investigations, and include the other conditions in which Kussmaul's sign appears to occur.

David H. Spodick, MD, DSc
Worcester, Massachusetts
15 November 1989

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Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

Living with Mitral Valve Prolapse

What Roberts¹ said about a congenitally bicuspid aortic valve in his recent editorial can be equally applicable to mitral valve prolapse. As he also pointed out in 1984,² mitral valve prolapse and bicuspid aortic valve are the 2 most common congenital heart diseases. Just as in the case of bicuspid aortic valve, mitral valve prolapse became diagnosed in increasing frequency since the introduction of echocardiography into clinical medicine.³ Unfortunately, echocardiography also leads to overdiagnosis and unnecessary concern in many instances. Since mitral valve prolapse is such a prevalent condition throughout the world,⁴ it has to be a benign condition in most instances unless certain complications occur.⁵⁻⁷

Thus, "the echocardiogram will continue to detect abnormalities in the heart that at the time cause no trouble. As a consequence, this instrument at times will produce worry and concern in both patient and physician."¹ Persons can certainly not only live with mitral valve prolapse but also be living and well.

Tsung O. Cheng, MD
Washington, DC
15 December 1989

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7. Cheng TO. Mitral valve prolapse. *Annu Rev Med* 1989;40:201-211.

Exercise Testing for Right Ventricular Ischemia

Reference is made to the article by Chouhan et al entitled "Utility of Lead V₄R in Exercise Testing for Detection of Coronary Artery Disease." The authors were apparently unaware of our study² of the same subject. In our study the right precordium was explored using V₆R as well as V₄R. The sensitivity of significant exercise induced ST deviation in both V₆R and V₄R for right coronary disease was 61.9% (compared to 32% using only V₄R in the study of Chouhan et al), and the specificity was 80% (compared to 88% in the study of Chouhan et al). In addition, in 4 patients exercise-induced ST-segment abnormality was found only in lead V₆R.

We agree with Chouhan et al that right chest leads are useful in detecting transient right ventricular ischemia due to right coronary artery disease during exercise testing. We suggest that the sensitivity of the method may be substantially increased by using precordial lead V₆R as well as V₄R without significant reduction in specificity.

Shirley Rubler, MD
Martin Dolgin, MD
New York, New York
15 November 1989

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Butterfat and the Navy Ration Law

The need to reduce fat and cholesterol in the American diet is now obvious. The diet recommendations made by the National Heart, Lung, and Blood Institute consensus panel represent a prudent first step for the general population. Although much effort is now being spent on public education, physicians are also challenged to identify institutional practices, occasionally written into law, that perpetuate an unhealthy intake of fat and cholesterol.

The Navy Ration Law found in Title 10, United States Code, Section 6082, traces its roots to an Act passed by the Third Congress on March 27, 1792.¹ This law provided that on Wednesdays sailors were to receive 2 ounces of butter in their daily ration. Although the Navy Ration Law was amended over the years, the last time in 1933, it still provides each sailor "one and six-tenths ounces of butter." This law has been interpreted by the Navy to prohibit the purchase of margarine for Navy messes both ashore and afloat. While we can appreciate the Third Congress' concern for the menu of a sloop of war, this hoary proscription against low-fat and low-cholesterol margarine is certainly counter to the health of the men and women of today's Navy.

Our concerns are shared by higher authority. Efforts are underway to bring this to Congressional attention. Needed legislation, however, may require a heightened awareness that current mandated dietary practices will lead to high costs in disease, disability and death.

Rodney W. Savage, MD
Robert Masci, MD

Portsmouth, Virginia
4 May 1990

1. Deschauer J (Lieutenant Commander, United States Navy). Personal communication. April 20, 1990.

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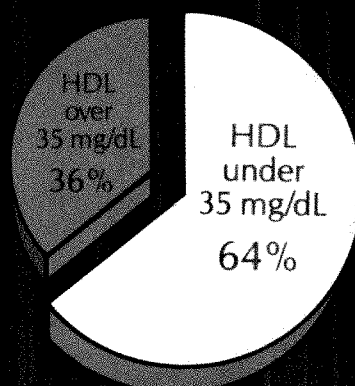
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<35 HDL
mg/dL

What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol and triglycerides—are common among heart attack victims,¹ and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.²

HEART ATTACK PATIENTS
(PROCAM TRIAL)²



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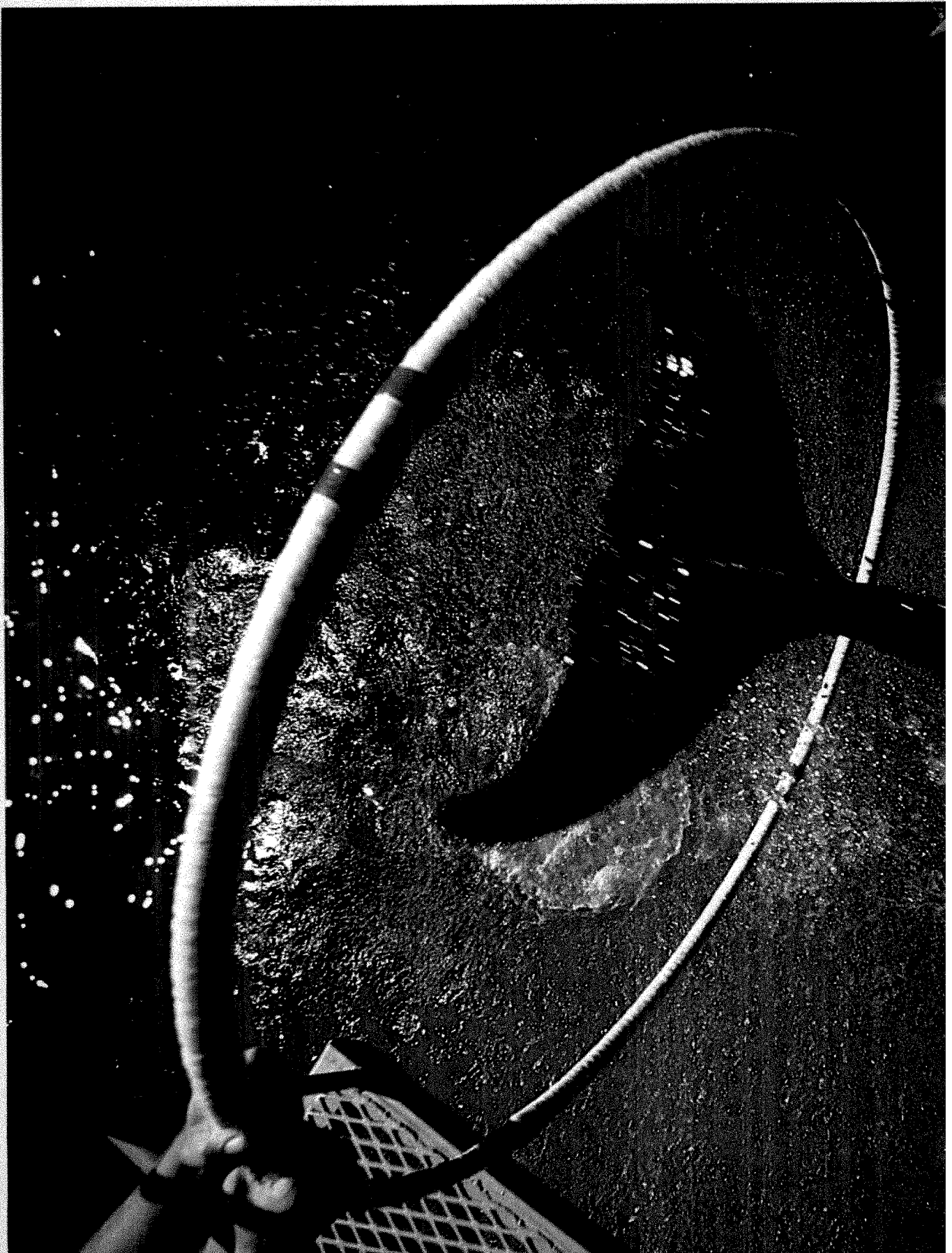
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CORONARY ARTERY DISEASE**529****Role of Left Ventricular Dysfunction in Selective Neurohumoral Activation in the Recovery Phase of Anterior Wall Acute Myocardial Infarction**

Douglas E. Vaughan, Gervasio A. Lamas, and Marc A. Pfeffer

In this study, the neurohumoral profiles of 36 asymptomatic patients in the early convalescent phase after acute myocardial infarction were examined. All patients in the study had a radionuclide ejection fraction $\leq 45\%$ and underwent cardiac catheterization 11 to 30 days after infarction. Activation of the renin-angiotensin-aldosterone system can be identified in hemodynamically compensated postinfarction patients not taking diuretics and appears to be related to the extent of left ventricular dysfunction.

533**Prevalence, Incidence and Prognosis of Recognized and Unrecognized Myocardial Infarction in Persons Aged 75 Years or Older: The Bronx Aging Study**

Jeremy Nadelmann, William H. Frishman, Wee Lock Ooi, David Tepper, Steven Greenberg, Howard Guzik, Eliot J. Lazar, Mark Heiman, and Miriam Aronson

We assessed the prevalence, incidence and prognosis of recognized and unrecognized Q-wave myocardial infarction in a cohort of 390 non-demented, "old old" subjects without terminal disease at entry. Old old subjects with prior evidence of MI, irrespective of presentation, have a worse outcome compared with those having no evidence of MI.

538**Randomized Controlled Trial of Late In-Hospital Angiography and Angioplasty Versus Conservative Management After Treatment with Recombinant Tissue-Type Plasminogen Activator in Acute Myocardial Infarction**

Gabriel I. Barbash, Arie Roth, Hanoeh Hod, Michaela Modan, Hilton I. Miller, Shemuel Rath, Yedahel Har Zahav, Gad Keren, Michael Motro, Amir Shachar, Samuel Basan, Oren Agranat, Babeth Rabinowitz, Shlomo Laniado, and Elieser Kaplinsky

Two hundred and one patients with acute myocardial infarction were randomized to the invasive group (97 patients) with routine coronary angiography and angioplasty 5 ± 2 days after thrombolytic therapy or to the conservative group (104 patients) with angiography only for recurrent postinfarction or exercise-induced ischemia. In the invasive group, 92 patients

underwent angiography, 49 angioplasty and 11 coronary artery bypass surgery, and in the conservative group, 40 patients had early ischemia, 39 underwent angiography, 20 angioplasty and 4 coronary artery bypass surgery. Our data indicate that conservative treatment is preferable to invasive treatment, even when cardiac catheterization is delayed.

546**Prognostic Use of a QRS Scoring System After Hospital Discharge for Initial Acute Myocardial Infarction in the Framingham Cohort**

Michael G. Jones, Keaven M. Anderson, Peter W. F. Wilson, William B. Kannel, Nancy B. Wagner, and Galen S. Wagner

We assessed the prognostic value of AMI size as estimated by the Selvester QRS score in 243 patients with an initial AMI from the original Framingham Heart Study cohort. Identification of AMI survivors at high risk for subsequent mortality can be improved by routine blood pressure measurement before AMI, and by QRS scoring of the electrocardiogram taken at the time of AMI hospital discharge.

551**Comparison of Early Exercise Treadmill Test and Oral Dipyridamole Thallium-201 Tomography for the Identification of Jeopardized Myocardium in Patients Receiving Thrombolytic Therapy for Acute Q-Wave Myocardial Infarction**

Avanindra Jain, Rachelle R. Hicks, Diane M. Frantz, G. Hunter Myers, and Matthew W. Rowe

In 46 patients who received thrombolytic therapy for acute Q-wave myocardial infarction, we performed early symptom-limited exercise stress tests and thallium-201 tomography using oral dipyridamole without complications. Thallium tomography identified more patients with ischemia; therefore, it may be superior for the identification of high-risk patients.

556**Coronary Collaterals Assessed with Myocardial Contrast Echocardiography in Healed Myocardial Infarction**

Young-Jae Lim, Shinsuke Nanto, Tohru Masuyama, Kazuhisa Kodama, Akio Kohama, Akira Kitabatake, and Takenobu Kamada

We performed myocardial contrast echocardiography to assess coronary collaterals in 29 patients with old myocardial infarction. Parameters of MCE were compared with angiographic grades of coronary collaterals and of wall motion abnormalities. MCE may provide a measure of the collateral perfusion, which may reflect the activity of collaterals better than the angiographic grading.

562

Morphometric Analysis of the Composition of Coronary Arterial Plaques in Isolated Unstable Angina Pectoris with Pain at Rest

Amy H. Kragel, Shanthasundari G. Reddy, Janet T. Wittes, and William C. Roberts

In 10 patients with isolated unstable angina pectoris with pain at rest, we studied coronary artery plaque morphology in 354 five-mm segments of the 4 major epicardial coronary arteries. The major component of plaque in patients with unstable angina is fibrous tissue.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

568

Relation of Peri-Infarction Block to Ventricular Late Potentials in Patients with Inferior Wall Myocardial Infarction

Nancy C. Flowers, Leo G. Horan, Anita C. Wylds, Wynne Crawford, Marandapalli R. Sridharan, C. Paige Horan, and Sandra F. Cliff

We obtained signal-averaged electrocardiograms on 70 patients with inferior wall myocardial infarction, divided into those with (23) and those without (47) peri-infarction block. The incidence of late potentials combined with ventricular arrhythmias in patients with peri-infarction block suggests that the presence of the peri-infarction block pattern on the surface electrocardiogram may provide another marker for identifying persons at increased risk for sustained ventricular arrhythmias subsequent to myocardial infarction.

575

Comparison of Right Ventricular Impedance, Pulse Pressure and Maximal dP/dt for Determination of Hemodynamic Stability of Ventricular Arrhythmias Associated with Coronary Artery Disease

Mark A. Wood, Kenneth A. Ellenbogen, Ketan Kapadia, Bin Lu, and Harry Valenta

We measured right ventricular impedance, RV pulse pressure, maximal systolic RV dP/dt and cycle length before, during and after 27 episodes of ventricular tachyarrhythmias induced in 17 patients. Hemodynamic parameters such as RV pulse pressure and impedance may be useful in future implantable antitachycardiac devices for discriminating hemodynamically stable from unstable ventricular tachycardia.

SYSTEMIC HYPERTENSION

583

Risk Stratification of Left Ventricular Hypertrophy in Systemic Hypertension Using Noninvasive Ambulatory Blood Pressure Monitoring

Paolo Verdecchia, Giuseppe Schillaci, Francesca Boldrini, Massimo Guerrieri, Camillo Gatteschi, Guglielmo Benemio, and Carlo Porcellati

One hundred sixty-five untreated hypertensive patients were classified according to the difference between their observed and their predicted average 24-hour ambulatory blood pressure level (the latter assessed by regressing the observed ambulatory BP on the casual BP.) Compared to those with lower than predicted ambulatory BP (≤ 10 mm Hg for systolic and ≤ 6 mm Hg for diastolic BP), patients with higher than predicted ambulatory BP (≥ 10 mm Hg for systolic and ≥ 6 mm Hg for diastolic BP) had higher values of left ventricular mass index and other indexes of LV hypertrophy (all $p < 0.01$), but

similar values of casual BP. Thus, hypertensive patients whose ambulatory BP readings are notably higher than one would predict from clinical BP readings are at highest risk of LV hypertrophy, an independent prognostic marker.

591

Cardiac and Skeletal Muscle Adaptations to Training in Systemic Hypertension and Effect of Beta Blockade (Metoprolol or Propranolol)

Philip A. Ades, Peter G.S. Gunther, William L. Meyer, Thomas C. Gibson, John Maddalena, and Thomas Orfeo

We studied 30 hypertensive adults who entered an exercise program taking either placebo, metoprolol or propranolol. The placebo group increased aerobic capacity 24% with minimal changes in cardiac size and function. The group taking metoprolol increased $\dot{V}O_{2\max}$ 8% and reduced resting blood pressure and total systemic resistance, whereas those taking propranolol had no increase in $\dot{V}O_{2\max}$, no decrease in resting blood pressure and no cardiovascular or peripheral adaptations to the exercise program.

597

Pattern of Peripheral Venous Response to Volume Expansion in Borderline Systemic Hypertension

Claudio Borghi, Stefano Boschi, Francesco Vittorio Costa, and Ettore Ambrosioni

The hemodynamic and humoral effects of acute intravenous sodium chloride loading was studied in a group of 25 borderline hypertensive patients with a different pattern of baseline venous distensibility (VV30). Results of this study suggest the ability of acute volume expansion to decrease peripheral venous distensibility in borderline hypertensive patients. The extent of vasoconstrictive response is related to the increase in plasma levels of an endogenous sodium ion/potassium ion adenosine triphosphatase inhibitor.

CONGESTIVE HEART FAILURE

603

Usefulness of Bucindolol in Congestive Heart Failure

Stewart G. Pollock, John Lystash, Christine Tedesco, George Craddock, and Mark L. Smucker

To determine whether bucindolol is an effective treatment for congestive heart failure, 19 patients with CHF were randomized to bucindolol ($n = 12$) or placebo ($n = 7$) in a double-blind protocol. With active treatment, exercise time, questionnaire score, ejection fraction, cardiac output and systemic vascular resistance significantly improved; no effect was seen in the placebo group. Thus, bucindolol is an effective treatment for CHF and its nonadrenergic vasodilation may be an important feature.

608

Failure of Captopril to Prevent Nitrate Tolerance in Congestive Heart Failure Secondary to Coronary Artery Disease

Nader Dakak, Nabeel Makhoul, Moshe Y. Flugelman, Amnon Merdler, Habib Shehadeh, Adam Schneeweiss, David A. Halon, and Basil S. Lewis

What is the role of angiotensin-converting enzyme inhibition in preventing or minimizing tolerance to intravenous nitroglycerin in severe congestive heart failure? We quantitated the degree of tolerance in 12 patients receiving nitroglycerin (group 1) and in 9 patients (group 2) receiving nitroglycerin and concurrent treatment with captopril (60 ± 29 mg daily). The ex-

tent of tolerance to high-dose intravenous nitroglycerin in CHF was unaltered by administration of captopril, indicating that in clinical dosage, counter-regulatory neurohumoral mechanisms involving the renin-angiotensin system appear to be unimportant in its development.

VALVULAR HEART DISEASE

614

Analysis of Different Methods of Assessing the Stenotic Mitral Valve Area with Emphasis on the Pressure Gradient Half-Time Concept

Bengt Wranne, Per Ask, and Dan Loyd

This study summarizes 2 different theoretical models that analyze factors influencing the transmitral pressure gradient half-time. Both models predict that half-time is influenced not only by valve area, but also by initial maximal pressure gradient and by flow. Different clinical situations in which the half-time method does not work are analyzed in terms of the 2 models.

621

Evaluation of Mitral Regurgitation by Cine Magnetic Resonance Imaging

Gerard Aurigemma, Nathaniel Reichek, Mark Schiebler, and Leon Axel

We used cine magnetic resonance imaging to assess mitral regurgitation in 40 patients with coronary and/or valvular disease and 10 normal subjects and compared results to pulsed ($n = 30$) or color flow Doppler mapping ($n = 20$). Planar analysis of cine MRI in patients with MR of varying severity gave results that were similar to Doppler echocardiography. At present, for routine clinical assessment of MR, the benefits of cine MRI may be limited to patients in whom transthoracic Doppler echocardiography is inadequate.

CARDIOMYOPATHY

627

Genetic Evidence of Dissociation (Generational Skips) of Electrical from Morphologic Forms of Hypertrophic Cardiomyopathy

Neal D. Epstein, Henry J. Lin, and Lameh Fananapazir

We studied 5 adult subjects in 4 families who are obligate or highly probable carriers of the hypertrophic cardiomyopathy gene by virtue of their position in the pedigree, but who have normal echocardiographic findings. Data indicate that the spectrum of HC includes persons who have a potentially arrhythmogenic left ventricular substrate but who have no evidence of left ventricular hypertrophy; "generational skips" also imply that some instances of HC may be familial.

MISCELLANEOUS

632

One Heart, Two Bodies: Insight from the Transplanted Heart and Its New Electrocardiogram

Samuel M. Butman, Brendan Phibbs, Joan Wild, and Jack G. Copeland

To address questions on the effect of rotation of the heart on its long axis on the surface electrocardiogram, the effect of thoracic anatomy on ECG voltage and predisposing factors for conduction defects observed after transplant surgery, we re-

viewed a series of 35 matched donor and recipient ECGs. There were no differences in the mean height of the donors and recipients, but age, weight and body surface area were higher in the recipients ($p < 0.025$). Age and body habitus, per se, do not appear to affect precordial voltage, and evidence of right bundle delay in the transplant recipient appears to be related to the altered position of the heart and not to injury or changes in right ventricular hemodynamics.

CARDIOVASCULAR PHARMACOLOGY

636

Effects of Bepridil and CERM 4205 (ORG 30701) on the Relation Between Cardiac Cycle Length and QT Duration in Healthy Volunteers

Brigitte Lecocq, Vincent Lecocq, Pierre-Louis Prost, Odile Fleurot, Pierre Boisson, and Patrice Jaillon

This study compared the effects of bepridil and CERM 4205 on the QT-RR relation at different heart rates during rest and exercise and the results of pharmacologic tests designed to vary neurovegetative tone. Only bepridil significantly prolonged QT duration, and the bepridil-induced prolongation of the QT interval was rate-dependent and increased at slow heart rates, which could explain the greater incidence of torsades de pointes in sinus bradycardia.

EDITORIAL

642

Are Electrophysiologic Studies Indicated in Nonsustained Ventricular Tachycardia?

Isaac Wiener, William Stevenson, James Weiss, and Koonlawee Nadamanee

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Effect of Left Ventricular Ejection Fraction on Malfunctioning St. Jude Medical Prosthesis in the Aortic Valve Position

Jian-Fang Ren, Gary S. Mintz, Krishnaswamy Chandrasekaran, John J. Ross, Jr, Ronald S. Pennock, and William S. Frankl

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Analysis of Heart Rate Changes in Cardiac Transplant Recipients Related to Graft Rejection

Gottfried Heinz, Günther Laufer, Thomas Öhner, Slobodan Gasic, and Axel Laczkovics

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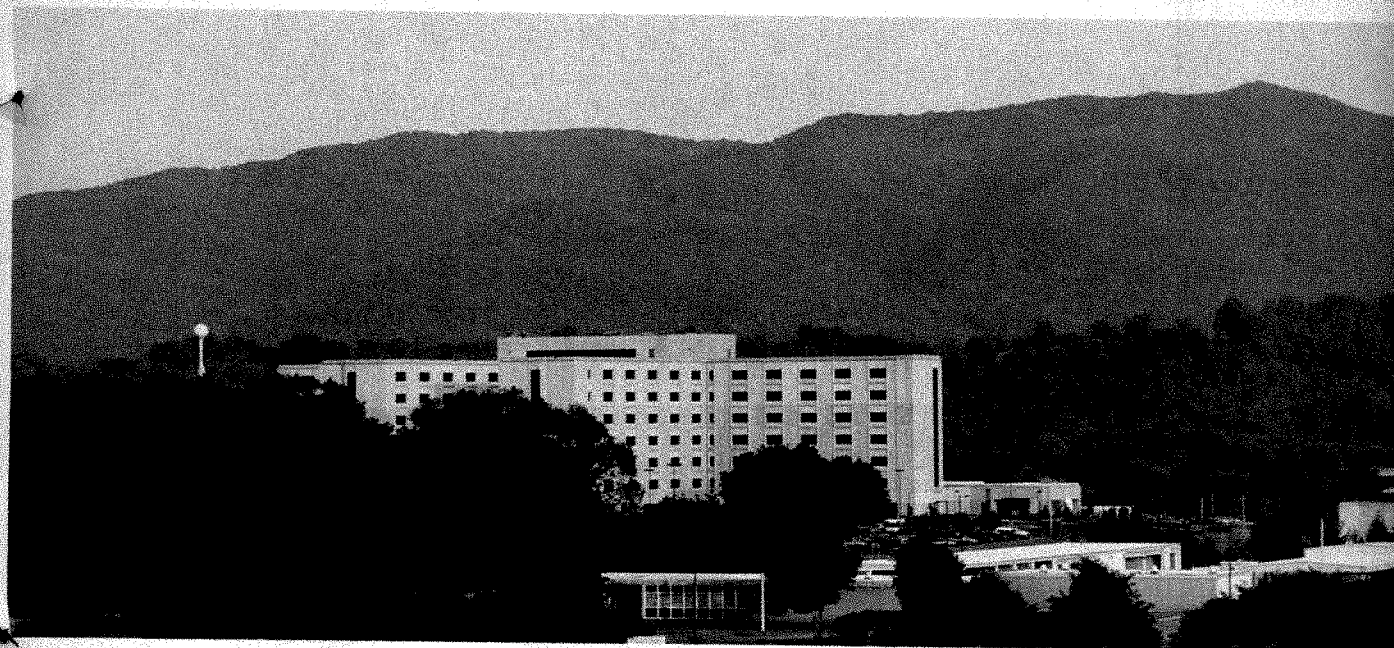
Failure of Trifluoperazine to Resolve Spontaneous Echo Contrast Evaluated by Transesophageal Echocardiography

Rainer Hoffmann, Heinz Lambertz, Andreas Kreis, and Peter Hanrath

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CLASSIFIED ADVERTISING on page A22, A45, A49, A82

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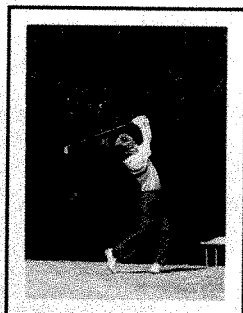
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CORONARY ARTERY DISEASE

529**Role of Left Ventricular Dysfunction in Selective Neurohumoral Activation in the Recovery Phase of Anterior Wall Acute Myocardial Infarction**

Douglas E. Vaughan, Gervasio A. Lamas, and Marc A. Pfeffer

Neurohumoral activation is readily apparent in patients with symptomatic congestive heart failure and in the acute phase after acute myocardial infarction. In this study, the neurohumoral profiles of 36 asymptomatic patients in the early convalescent phase after acute myocardial infarction were examined. All patients in the study had a radionuclide ejection fraction $\leq 45\%$ and underwent cardiac catheterization 11 to 30 days after infarction. Despite the reduced ejection fraction and extensive wall motion abnormalities, plasma norepinephrine was not elevated and did not correlate with any measured hemodynamic, angiographic or clinical variables. The renin-angiotensin II-aldosterone system was activated, as expected, in the 9 study patients receiving loop diuretics. However, even in the 27 patients not receiving diuretics, plasma angiotensin II levels and plasma renin activity levels were increased in relation to Killip classification, the presence of a left ventricular aneurysm and the left ventricular ejection fraction. Activation of the renin-angiotensin-aldosterone system can be identified in hemodynamically compensated postinfarction patients not taking diuretics. This activation appears to be related to the extent of left ventricular dysfunction.

533**Prevalence, Incidence and Prognosis of Recognized and Unrecognized Myocardial Infarction in Persons Aged 75 Years or Older: The Bronx Aging Study**

Jeremy Nadelmann, William H. Frishman, Wee Lock Ooi, David Tepper, Steven Greenberg, Howard Guzik, Eliot J. Lazar, Mark Heiman, and Miriam Aronson

The prevalence, incidence and prognosis of recognized and unrecognized Q-wave myocardial infarction (MI) were assessed in a cohort of 390 nondemented, "old old" subjects without terminal disease at entry. At baseline, 34.7% of all detectable MIs were previously unrecognized. During 8 years of follow-up, there was a 2.4/100 person-years rate of unrecognized

Continued on page A15

variables, was assessed in 243 patients with an initial AMI from the original Framingham Heart Study cohort. QRS score and an elevated systolic blood pressure before the AMI were found to be the variables most significantly associated ($p < 0.05$) with time until coronary heart disease-related death. Identification of AMI survivors at high risk for subsequent mortality can be improved by routine blood pressure measurement before AMI, and by QRS scoring of the electrocardiogram taken at the time of AMI hospital discharge.

551

Comparison of Early Exercise Treadmill Test and Oral Dipyridamole Thallium-201 Tomography for the Identification of Jeopardized Myocardium in Patients Receiving Thrombolytic Therapy for Acute Q-Wave Myocardial Infarction

Avanindra Jain, Rachelle R. Hicks, Diane M. Frantz, G. Hunter Myers, and Matthew W. Rowe

We performed early symptom-limited exercise stress tests and thallium-201 tomography using oral dipyridamole in 46 patients who received thrombolytic therapy for acute Q-wave myocardial infarction. There were no complications during either study. During exercise stress test, 13 patients had a positive response and 10 additional patients had angina. After dipyridamole 34 patients had evidence for ischemia. Thus, functional tests were performed without complications early after myocardial infarction. Thallium tomography identified more patients with ischemia; therefore, it may be superior for the identification of high-risk patients.

556

Coronary Collaterals Assessed with Myocardial Contrast Echocardiography in Healed Myocardial Infarction

Young-Jae Lim, Shinsuke Nanto, Tohru Masuyama, Kazuhisa Kodama, Akio Kohama, Akira Kitabatake, and Takenobu Kamada

Myocardial contrast echocardiography (MCE) was performed to assess the coronary collaterals in 29 patients with old myocardial infarction. Parameters of MCE were compared with coronary angiographic grades of collaterals and left ventricular graphic grades of wall motion abnormalities. The degree of enhancement of MCE in the infarct area generally corresponded to the collateral grades with coronary angiography. However, there were a few patients with low enhancement of MCE despite good collaterals, which showed severe asynergy. MCE may provide a measure of the collateral perfusion, which possibly reflects the activity of collaterals better than the angiographic grading.

562

Morphometric Analysis of the Composition of Coronary Arterial Plaques in Isolated Unstable Angina Pectoris with Pain at Rest

Amy H. Kragel, Shanthasundari G. Reddy, Janet T. Wittes, and William C. Roberts

In 10 patients with isolated unstable angina pectoris with pain at rest, we studied coronary artery plaque morphology in 354 five-mm segments of the 4 major epicardial coronary arteries. The major component of plaque in patients with unstable angina is fibrous tissue.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

568

Relation of Peri-Infarction Block to Ventricular Late Potentials in Patients with Inferior Wall Myocardial Infarction

Nancy C. Flowers, Leo G. Horan, Anita C. Wylds, Wynne Crawford, Marandapalli R. Sridharan, C. Paige Horan, and Sandra F. Cliff

Seventy patients with inferior wall myocardial infarction were divided into those with (23) and those without (47) peri-infarction block. Signal-averaged electrocardiograms were obtained on each patient. There were 13 instances of sustained ventricular tachycardia, ventricular fibrillation or sudden death, 11 of which occurred in the peri-infarction group. Total duration of the vectormagnitude complex and the duration of terminal potential under 40 μ V in the peri-infarction group exceeded that in the group without peri-infarction block ($p < 0.0001$). The voltage in the last 40 ms was also significantly less in the peri-infarction group ($p < 0.0005$). The higher incidence of late potentials in the peri-infarction group combined with the higher incidence of sustained ventricular arrhythmias in the same group suggests that the presence of the peri-infarction block pattern on the surface electrocardiogram may provide another marker for identifying persons at increased risk for sustained ventricular arrhythmias subsequent to myocardial infarction.

575

Comparison of Right Ventricular Impedance, Pulse Pressure and Maximal dP/dt for Determination of Hemodynamic Stability of Ventricular Arrhythmias Associated with Coronary Artery Disease

Mark A. Wood, Kenneth A. Ellenbogen, Ketan Kapadia, Bin Lu, and Harry Valenta

Right ventricular (RV) impedance, RV pulse pressure, maximal systolic RV dP/dt and cycle length were measured before, during and after 27 episodes of ventricular tachyarrhythmias induced in 17 patients. Changes in these values from baseline levels were compared to changes in mean and systolic blood pressure accompanying the arrhythmias. Ventricular

Continued on page A24

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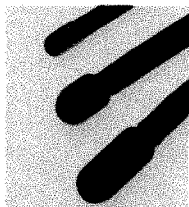
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tachycardia cycle length and the percent changes in RV impedance and RV pulse pressure correlated significantly with systemic hemodynamic changes during ventricular tachycardia ($p < 0.05$). The arithmetic product of impedance and RV pulse pressure correlated most closely with hemodynamic compromise ($r \geq 0.82$, $p < 0.001$). Hemodynamic parameters such as RV pulse pressure and impedance may be useful in future implantable antitachycardiac devices for discriminating hemodynamically stable from unstable ventricular tachycardia.

SYSTEMIC HYPERTENSION

583

Risk Stratification of Left Ventricular Hypertrophy in Systemic Hypertension Using Noninvasive Ambulatory Blood Pressure Monitoring

Paolo Verdecchia, Giuseppe Schillaci, Francesca Boldrini, Massimo Guerrieri, Camillo Gatteschi, Guglielmo Benemio, and Carlo Porcellati

One hundred sixty-five untreated hypertensive patients were classified according to the difference between their observed and their predicted average 24-hour ambulatory blood pressure (BP) level (the latter assessed by regressing the observed ambulatory BP on the casual BP). Compared to those with lower than predicted ambulatory BP (≤ 10 mm Hg for systolic and ≤ 6 mm Hg for diastolic BP), patients with higher than predicted ambulatory BP (≥ 10 mm Hg for systolic and ≥ 6 mm Hg for diastolic BP) had higher values of left ventricular (LV) mass index and other indexes of LV hypertrophy (all $p < 0.01$), but similar values of casual BP. Prevalence of LV hypertrophy was 6 to 10% in the former and 35 to 39% in the latter patients ($p < 0.001$). None of the echocardiographic indexes of LV structure differed between the low ambulatory BP group and a control group of 92 healthy subjects. Thus, hypertensive patients whose ambulatory BP readings are notably higher than one would predict from clinical BP readings are at highest risk of LV hypertrophy, an independent prognostic marker. Noninvasive ambulatory BP monitoring identifies a subset of hypertensive patients in whom the routine echocardiographic examination of the left ventricle is recommended.

591

Cardiac and Skeletal Muscle Adaptations to Training in Systemic Hypertension and Effect of Beta Blockade (Metoprolol or Propranolol)

Phillip A. Ades, Peter G.S. Gunther, William L. Meyer, Thomas C. Gibson, John Maddalena, and Thomas Orfeo

Cardiovascular and peripheral adaptations to an aerobic conditioning program were studied in 30 hypertensive adults taking either placebo, β_1 -selective β -adrenergic blocker (metoprolol) or β_1 -nonselective β -adrenergic blocker (propranolol). The placebo group increased aerobic capacity ($\dot{V}O_{2\max}$) by 24% ($p < 0.002$), largely explained by an increased peripheral arteriovenous (A-V) oxygen difference with minimal changes in cardiac size and function. Resting blood pressure and total systemic resis-

Continued on page A26



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tance were decreased as well. The group taking β_1 -selective β blocker increased aerobic capacity by 8% ($p < 0.05$), reduced resting blood pressure but had no significant change of A-V oxygen difference or cardiac size or function. The group taking the β_1 -nonselective β -blocker propranolol did not increase $\dot{V}O_{2\max}$, did not decrease resting blood pressure and had no cardiovascular or peripheral adaptations. Thus, β_1 -selective and β_1 -nonselective β blockers attenuate conditioning in hypertensive patients to differing degrees by blocking peripheral mechanisms of conditioning.

597

Pattern of Peripheral Venous Response to Volume Expansion in Borderline Systemic Hypertension

Claudio Borghi, Stefano Boschi, Francesco Vittorio Costa, and Ettore Ambrosioni

The hemodynamic and humoral effects of acute intravenous sodium chloride (NaCl) loading was studied in a group of 25 borderline hypertensive patients with a different pattern of baseline venous distensibility (VV30). Saline infusion elicited a generalized venoconstriction that was enhanced in patients with normal VV30 who also had a sudden increase in plasma levels of an endogenous sodium ion/potassium ion adenosine triphosphatase (Na^+/K^+ ATPase) inhibitor and a delayed atrial natriuretic factor response and renin suppression. The changes in plasma Na^+/K^+ ATPase inhibitory activity in response to NaCl were inversely related to those of VV30 in patients with normal VV30 ($r = -0.49$), whereas in the overall borderline hypertensive patients, they were not. A slight relation ($r = -0.42$) was found between atrial natriuretic peptide and Na^+/K^+ ATPase inhibitor responses in the whole hypertensive population. It suggested that acute volume expansion by saline is able to reduce peripheral venous distensibility in borderline hypertensive patients by increasing plasma levels of an endogenous Na^+/K^+ ATPase inhibitor whose release is strictly related either to delayed atrial natriuretic peptide stimulation or to sluggish renin suppression.

CONGESTIVE HEART FAILURE

603

Usefulness of Bucindolol in Congestive Heart Failure

Stewart G. Pollock, John Lystash, Christine Tedesco, George Craddock, and Mark L. Smucker

Bucindolol is a β blocker with intrinsic nonadrenergic vasodilation and may be an effective treatment for congestive heart failure (CHF). In a double-blind protocol, 19 patients with CHF were randomized to bucindolol ($n = 12$) or placebo ($n = 7$). With active treatment, exercise time, questionnaire score, ejection fraction, cardiac output and systemic vascular resistance significantly improved. Also, peak exercise pulmonary capillary wedge pressure decreased with treatment. No effect was seen in the placebo group. Thus, bucindolol is an effective treatment for CHF and its nonadrenergic vasodilation may be an important feature.

Continued on page A29

608

Failure of Captopril to Prevent Nitrate Tolerance in Congestive Heart Failure Secondary to Coronary Artery Disease

Nader Dakak, Nabeel Makhoul, Moshe Y. Flugelman, Amnon Merdler, Habib Shehadeh, Adam Schneeweiss, David A. Halon, and Basil S. Lewis

The possible role of angiotensin-converting enzyme inhibition in preventing or minimizing tolerance to intravenous nitroglycerin was examined in 21 patients with severe congestive heart failure (CHF), by quantitating nitrate tolerance in patients receiving and in those not receiving concurrent treatment with the angiotensin-converting enzyme inhibitor captopril (60 ± 29 mg daily). Intravenous nitroglycerin produced almost identical hemodynamic changes in both groups, with a reduction in right atrial and pulmonary arterial wedge pressure, an increase in cardiac index and decreases in systemic and pulmonary vascular resistance. Nitrate tolerance was calculated for each hemodynamic parameter as the percentage loss of peak benefit achieved by nitroglycerin. Nitrate tolerance ($\geq 50\%$ loss of efficacy) developed after 12 to 24 hours in almost identical fashion in a third to two-thirds of patients in both groups. The extent of tolerance was unaltered by captopril, indicating that in clinical dosage, counter-regulatory neurohumoral mechanisms involving the renin-angiotensin system appear to be unimportant in the development of nitrate tolerance in patients with CHF. The study also showed that considerable hemodynamic benefit may be achieved by addition of high doses of nitroglycerin to the management of patients receiving an angiotensin-converting enzyme inhibitor.

VALVULAR HEART DISEASE

614

Analysis of Different Methods of Assessing the Stenotic Mitral Valve Area with Emphasis on the Pressure Gradient Half-Time Concept

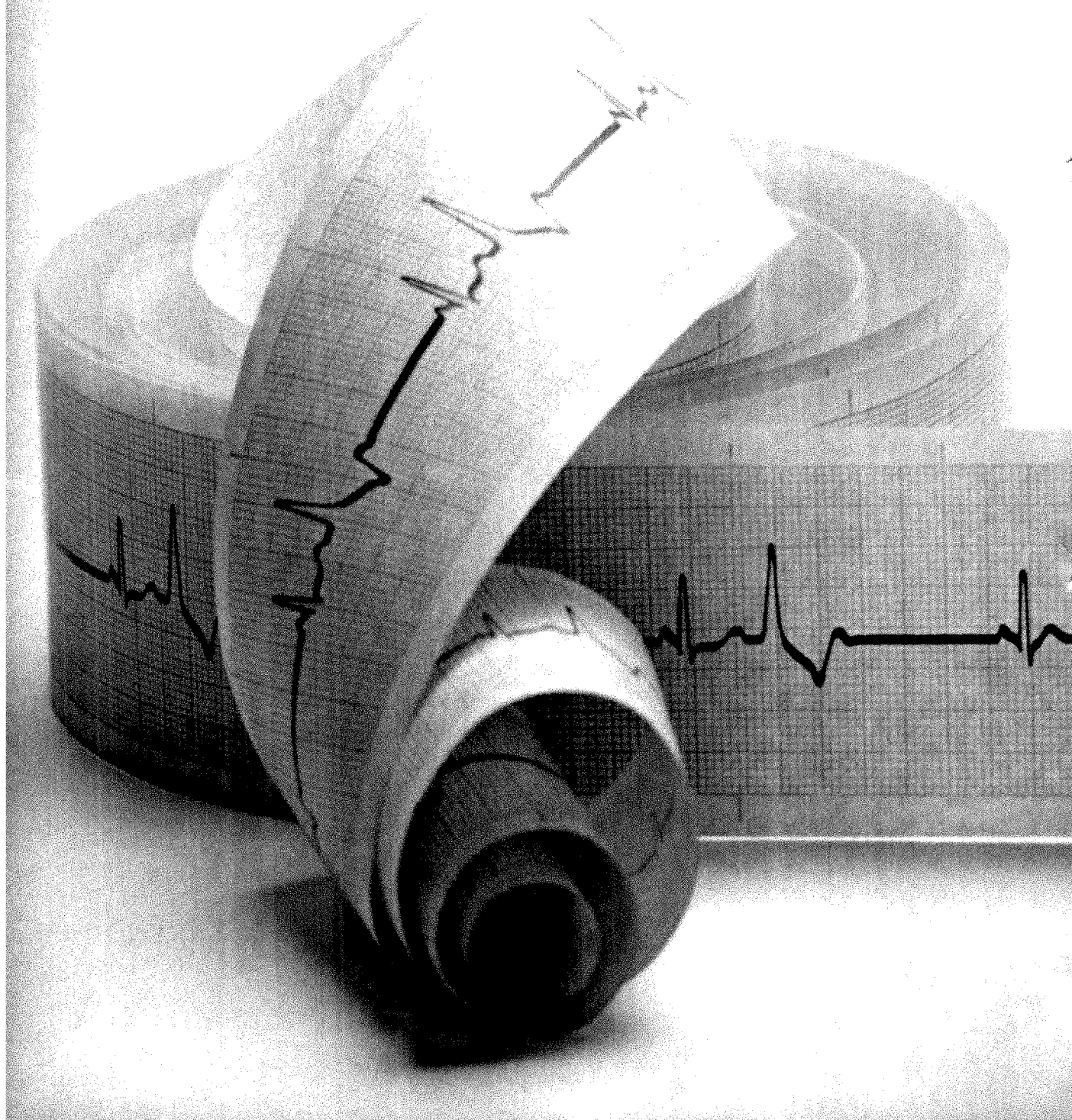
Bengt Wranne, Per Ask, and Dan Loyd

There are 2 different theoretical models that analyze factors influencing the transmitral pressure gradient half-time ($T_{1/2}$), defined as the time needed for the pressure gradient to reach half its initial value. This study summarizes the 2 models and the assumptions inherent in them. One model includes left heart chamber compliance and the other does not. Although the models at a superficial glance seem to be contradictory, conclusions drawn from them are similar; that is, $T_{1/2}$ is influenced not only by valve area, but also by initial maximal pressure gradient and by flow. Different clinical situations in which the $T_{1/2}$ method does not work are analyzed in terms of the 2 models. Based on this analysis, use of the continuity equation in these situations is advocated.

Continued on page A33

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621

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Gerard Aurigemma, Nathaniel Reichek, Mark Schiebler, and Leon Axel

We compared cine magnetic resonance imaging (cine MRI) grading of mitral regurgitation (MR) to pulsed or color flow Doppler in 40 patients with valvular and/or coronary artery disease and in 10 normal subjects. Cine MRI classification was identical to Doppler echocardiography in 42 of 50 subjects with no differences of >1 grade; there were no false positives (sensitivity 94%, specificity 100%). Though cine MRI consistently depicted smaller flow disturbances than Doppler echocardiography, the cine MRI jet area/left atrial area ratio (used to index regurgitation severity) correlated with pulsed ($r = 0.78$) and color flow Doppler ($r = 0.74$). Thus, planar analysis of cine MRI in patients with MR of varying severity gave results that were similar to Doppler echocardiography. For routine clinical assessment of MR, the benefits of cine MRI may be limited to patients in whom transthoracic Doppler echocardiography is inadequate.

CARDIOMYOPATHY

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Neal D. Epstein, Henry J. Lin, and Lameh Fananapazir

This study is a report of 5 adult subjects in 4 families who are obligate or highly probable carriers of the hypertrophic cardiomyopathy (HC) gene by virtue of their position in the pedigree, but who have normal echocardiographic findings. Four of these 5 subjects have abnormal signal-averaged electrocardiograms; this suggests the presence of electrical disease despite the absence of left ventricular (LV) hypertrophy. The fifth subject, an identical twin of a patient with familial HC, has neither LV hypertrophy nor a myocardial electrical abnormality. These data indicate that the spectrum of HC includes persons who have a potentially arrhythmogenic LV substrate but who have no evidence of LV hypertrophy. The demonstration of generational skips also implies that some instances of HC previously judged to be sporadic may be familial.

Continued on page A39

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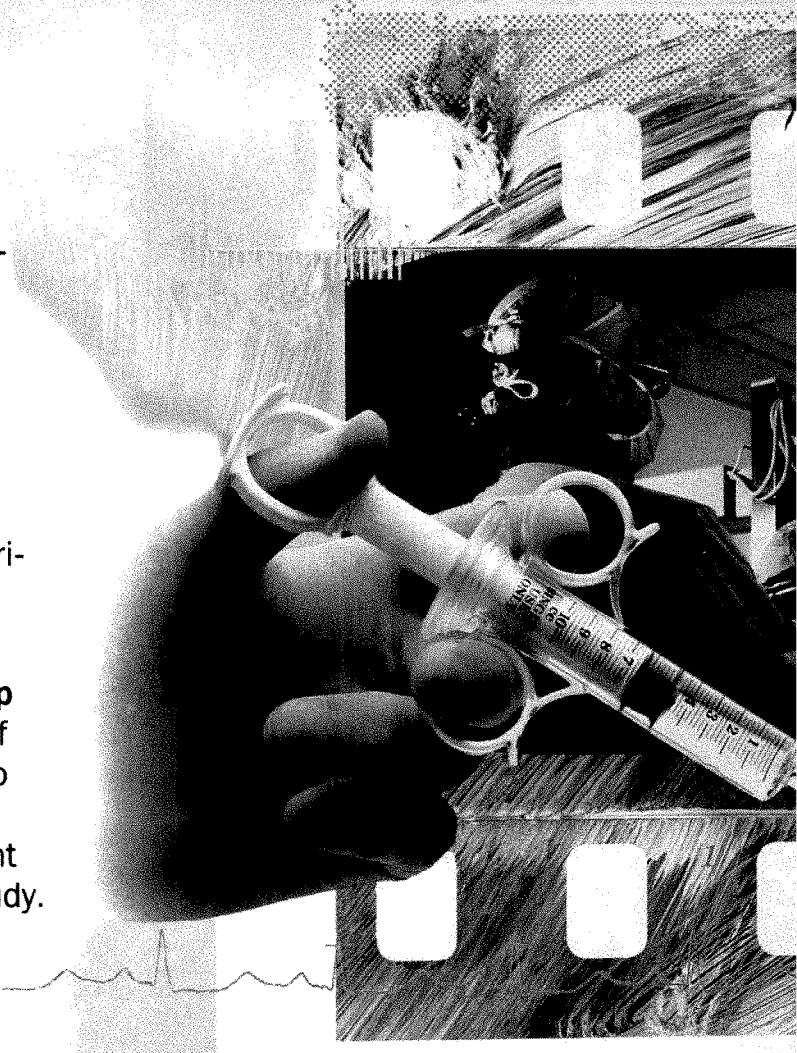
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MISCELLANEOUS

632**One Heart, Two Bodies: Insight from the Transplanted Heart and Its New Electrocardiogram**

Samuel M. Butman, Brendan Phibbs, Joan Wild, and Jack G. Copeland

Cardiac transplantation provides a unique opportunity to record the altered electrical field generated by a human heart in a new environment. A series of 35 matched donor and recipient electrocardiograms were reviewed to evaluate such changes. No significant differences were found in mean heart rate or precordial voltage, but the PR and QT intervals were shorter and the precordial transitional zone was more to the left after transplantation ($p < 0.0005$). New evidence of right bundle branch delay was found in 11 recipients, not related to pretransplantation hemodynamics or ischemic arrest. These findings suggest that there is indeed an anatomic basis for electrocardiographic evidence of clockwise rotation. Age and body habitus do not appear to affect precordial voltage and evidence of right bundle delay in the transplant recipient appears to be related to the altered position of the heart and not to injury or changes in hemodynamics.

CARDIOVASCULAR PHARMACOLOGY

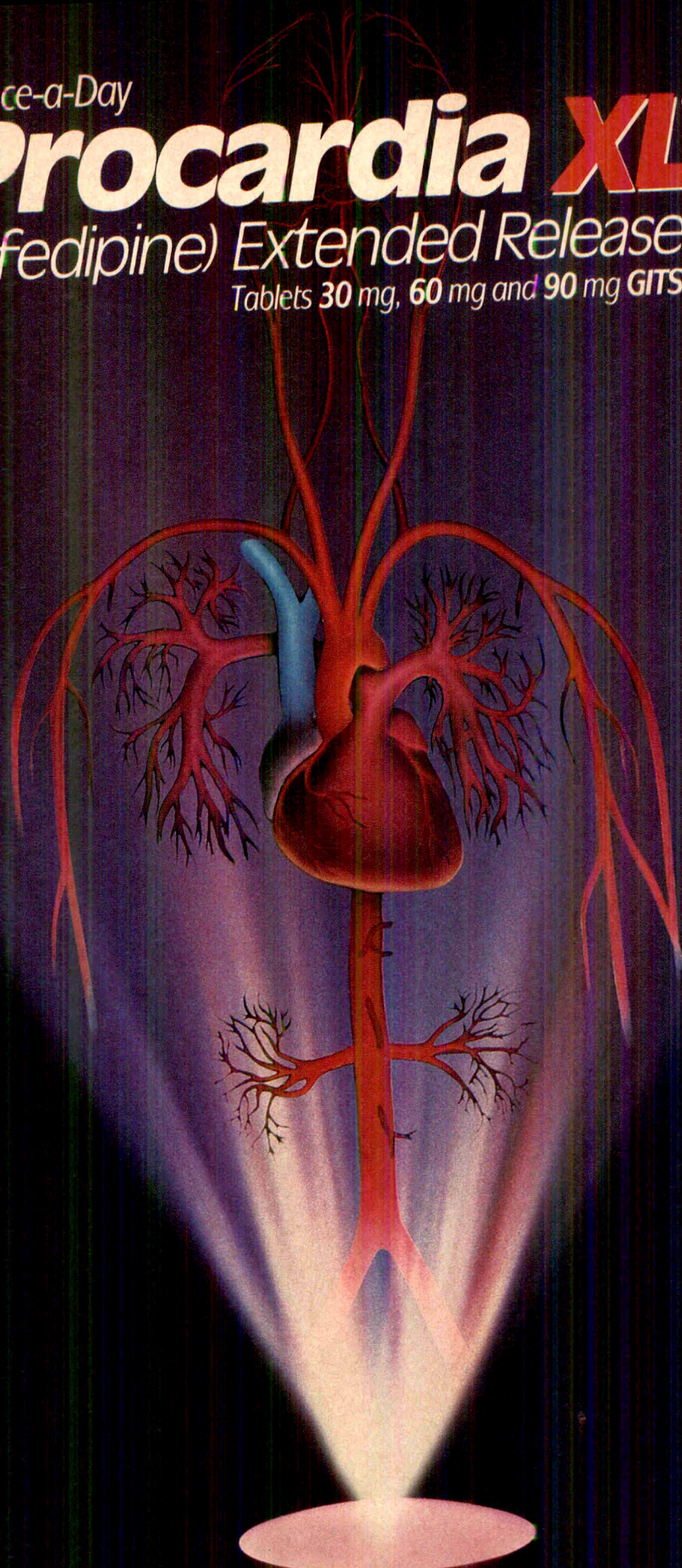
636**Effects of Bepridil and CERM 4205 (ORG 30701) on the Relation Between Cardiac Cycle Length and QT Duration in Healthy Volunteers**

Brigitte Lecocq, Vincent Lecocq, Pierre-Louis Prost, Odile Fleurot, Pierre Boisson, and Patrice Jaillon

In this randomized, double-blind, crossover, 3-period study, the effects of oral bepridil, CERM 4205 and placebo on the QT-RR relation were compared in 12 healthy volunteers during physiologic conditions (rest and exercise) and pharmacologic tests designed to vary neurovegetative tone. The results of the study suggested that (1) there was a distinct difference between bepridil and CERM 4205 with regard to their effects on ventricular repolarization—only bepridil significantly prolonged QT duration; and (2) the bepridil-induced prolongation of QT was rate-dependent and increased at slow heart rates, which could explain the greater incidence of torsades de pointes in sinus bradycardia.

Continued on page A46

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CardioGen-82[®] Rubidium Rb 82 Generator

INDICATIONS AND USAGE

Rubidium chloride Rb 82 injection is a myocardial perfusion agent that is useful in distinguishing normal from abnormal myocardium in patients with suspected myocardial infarction.

Cardiogen-82 (Rubidium Rb 82 Generator) must be used with an infusion system specifically labeled for use with the generator and capable of accurate measurement and delivery of doses of rubidium chloride Rb 82 injection not to exceed a single dose of 2220 MBq (60 mCi) and a cumulative dose of 4440 MBq (120 mCi) at a rate of 50 mL/min with a maximum volume per infusion of 100 mL and a cumulative volume not to exceed 200 mL. These performance characteristics reflect the conditions of use under which the drug development clinical trials were conducted.

Adequate data from clinical trials to determine precise localization of myocardial infarction or identification of stress-induced ischemia have not been collected.

Positron emission tomographic (PET) instrumentation is recommended for use with rubidium chloride Rb 82 injection.

CONTRAINDICATIONS

None known.

WARNINGS

Caution should be used during infusion as patients with congestive heart failure may experience a transitory increase in circulatory volume load. These patients should be observed for several hours following the Rb-82 procedure to detect delayed hemodynamic disturbances.

PRECAUTIONS

General

Data are not available concerning the effect of marked alterations in blood glucose, insulin, or pH (such as is found in diabetes mellitus) on the quality of rubidium chloride Rb 82 scans. Attention is directed to the fact that rubidium is physiologically similar to potassium, and since the transport of potassium is affected by these factors, the possibility exists that rubidium may likewise be affected.

Rubidium chloride Rb 82 injection must be administered only with an appropriate infusion system capable of meeting the performance characteristics previously described. (See INDICATIONS AND USAGE). The drug should be used only by those practitioners with a thorough understanding of the use and performance of the infusion system.

Repeat doses of rubidium chloride Rb 82 injection may lead to an accumulation of the longer lived radioactive contaminants strontium Sr 82 and strontium Sr 85.

Since eluate obtained from the generator is intended for intravenous administration, aseptic techniques must be strictly observed in all handling. Only additive free Sodium Chloride Injection USP should be used to elute the generator. Do not administer eluate from the generator if there is any evidence of foreign matter.

As in the use of any radioactive material, care should be taken to minimize radiation exposure to the patient consistent with proper patient management and to insure minimum radiation exposure to occupational workers.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed to evaluate carcinogenic potential, mutagenicity potential, or to determine whether rubidium Rb 82 may affect fertility in males or females.

Pregnancy Category C

Animal reproductive studies have not been conducted with rubidium Rb 82. It is also not known whether rubidium Rb 82 can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Rubidium Rb 82 should be given to pregnant women only if the expected benefits to be gained clearly outweigh the potential hazards.

Ideally, examinations using radiopharmaceuticals, especially those examinations which are elective in nature, in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.

Nursing Mothers

It is not known whether rubidium Rb 82 is excreted in human milk. Due to the short half-life of rubidium Rb 82 (75 sec) it is unlikely that the drug would be excreted in human milk during lactation. However, because many drugs are excreted in human milk, caution should be exercised when rubidium Rb 82 is administered to nursing women.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

No adverse reactions specifically attributable to rubidium Rb 82 have been reported during controlled clinical trials.

HOW SUPPLIED

Cardiogen-82 (Rubidium Rb 82 Generator) is supplied in the form of strontium Sr 82 adsorbed on a hydrous stannic oxide column with an activity of 90-150 millicuries Sr-82 at calibration time. The generator is encased in a lead shield surrounded by a labeled plastic container. Complete assay data for each generator are provided on the container label. Cardiogen-82 (Rubidium Rb 82 Generator) is intended for use only with an appropriate, properly calibrated infusion system labeled for use with the generator.

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Role of Left Ventricular Dysfunction in Selective Neurohumoral Activation in the Recovery Phase of Anterior Wall Acute Myocardial Infarction

Douglas E. Vaughan, MD, Gervasio A. Lamas, MD, and Marc A. Pfeffer, MD, PhD

Neurohumoral activation is readily apparent in patients with symptomatic congestive heart failure (CHF) and in the acute phase after acute myocardial infarction. In this study, the neurohumoral profiles of 36 asymptomatic patients in the early convalescent phase after acute myocardial infarction were examined. All patients in the study had a radionuclide ejection fraction $\leq 45\%$ and underwent cardiac catheterization 11 to 30 days after infarction. Venous blood samples were obtained in the supine state for the measurement of norepinephrine, angiotensin II, plasma renin activity and aldosterone in all patients. Despite the reduced ejection fraction and extensive wall motion abnormalities, plasma norepinephrine was not elevated and did not correlate with any measured hemodynamic, angiographic or clinical variables. The renin-angiotensin II aldosterone system was activated, as expected, in the 9 study patients receiving loop diuretics. However, even in the 27 patients not taking diuretics, plasma angiotensin II and renin activity levels were increased in relation to Killip classification, the presence of a left ventricular (LV) aneurysm and LV ejection fraction. Activation of the renin-angiotensin-aldosterone system can be identified in hemodynamically compensated postinfarction patients not taking diuretics and appears to be related to the extent of LV dysfunction.

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From the Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. This study was supported in part by a grant from E.R. Squibb & Sons and by Clinical Research Center Grant RR-02635 from the National Institutes of Health, Bethesda, Maryland. During the period of the study, Dr. Pfeffer was the recipient of an Established Investigator Award from the American Heart Association, Dallas, Texas. Dr. Lamas was recipient of training grant HL-07049 from the National Institutes of Health. Dr. Vaughan is the recipient of a Clinical Scientist Award from the American Heart Association. Manuscript received December 27, 1989; revised manuscript received and accepted April 27, 1990.

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Activation of neurohumoral systems that promote salt retention and vasoconstriction is a characteristic finding in patients with decompensated severe congestive heart failure (CHF).^{1,2} These systems include the renin-angiotensin-aldosterone and sympathetic nervous systems. Presumably, increased levels of these neurohormones help maintain cardiovascular homeostasis in the face of diminished cardiac output. The salt and water retention induced by these hormones in patients with CHF may be lessened somewhat by the counterregulatory effects of atrial natriuretic peptide, which is secreted from the atria in response to distension.^{3,4} In general, neurohumoral activation in patients with CHF appears to parallel the clinical severity of the disease.^{5,6} Marked increases in circulating norepinephrine appear to identify patients with an unfavorable long-term prognosis.⁷

Patients with a recent acute myocardial infarction (MI) demonstrate a broad spectrum of left ventricular (LV) dysfunction. A recent report described significant activation of the renin-angiotensin and sympathetic nervous system within 72 hours of acute MI.⁸ However, the presence and extent of neurohumoral activity in this population after completion of the acute event has not been completely characterized. This study determines the extent and pattern of neurohumoral activation in patients without symptomatic CHF after a first anterior wall acute MI.

METHODS

All patients were studied during the early convalescent phase of a first anterior wall acute MI resulting in an LV ejection fraction $\leq 45\%$ determined by radionuclide ventriculography. Patients aged 21 to 75 years were clinically stable and without overt CHF or active ischemia. The 36 patients included in this study comprise a subgroup from a previously described study⁹ in which neurohumoral profiling could be obtained under standardized conditions.

Study protocol: Patients underwent baseline cardiac catheterization between 11 and 30 days from the time of acute MI. Hemodynamic measurements, coronary angiography and biplane left ventriculography were performed in all patients. Cardiac outputs were determined by the Fick method. Left ventricular volumes were calculated from the biplane views using the area-length regression equation developed from heart casts.¹⁰ Biplane

TABLE I Baseline Characteristics of the Study Population (n = 36)

End-diastolic volume (ml)	231 ± 35
End-systolic volume (ml)	138 ± 41
Akinesia and dyskinesia ≥30 (%)	33
LV aneurysm (%)	56
Right atrial mean (mm Hg)	6 ± 2
Pulmonary artery wedge mean (mm Hg)	13 ± 6
LV diastolic (mm Hg)	21 ± 7
Arterial mean (mm Hg)	80 ± 9
Systolic	105 ± 14
Diastolic	62 ± 7
Cardiac index (liters/min/m ²)	2.7 ± 0.8

Values are expressed as mean ± standard deviation where applicable.
LV = left ventricular.

regional wall motion abnormality was calculated as the percentage of the diastolic perimeter that remained akinetic or dyskinetic during systole as previously described.¹¹ LV aneurysm was defined as being present when anterolateral and apical akinesia or dyskinesia as well as a clear diastolic deformity of LV contour were identified.¹²

Before cardiac catheterization, neurohumoral sampling for norepinephrine, angiotensin II, plasma renin activity, aldosterone, vasopressin and atrial natriuretic peptide was performed in the supine state 30 minutes after the insertion of an indwelling venous cannula. Plasma was separated from whole blood by centrifugation and frozen at -20°C until assayed. Plasma renin activity and aldosterone levels were determined by radioimmunoassays.^{13,14} Plasma angiotensin II was measured according to the method of Emanuel et al.¹⁵ Plasma norepinephrine was determined by an enzymatic assay.¹⁶ Radioimmunoassays were also used for the measurement of plasma atrial natriuretic peptide and vasopressin levels.^{17,18}

Statistical analysis: Comparisons between groups for continuous variables were made using a 1-way analysis of variance and the chi-square test was used for analyses of categorical variables. Correlations between continuous variables were determined using standard linear regression analyses. All data are presented as mean ± standard deviation and statistical significance was defined as $p < 0.05$ (2-tailed).

RESULTS

The baseline characteristics of the 36 study patients are summarized in Table I. Cardiac catheterization was performed 19 ± 6 days after the first acute MI. Eighteen of 36 subjects (50%) met clinical criteria for Killip classification ≥ 2 within 72 hours of acute MI. Twenty-five percent of the study patients were receiving diuretics while more than half of the patients were being treated with β -adrenergic blocking agents and no patients were receiving an angiotensin-converting enzyme inhibitor.

Left ventriculography revealed that both the diastolic and systolic volumes increased and over half of the patients had discrete LV aneurysms. Quantitative wall motion analysis indicated that one-third of the study patients had extensive wall motion abnormalities with per-

TABLE II Comparison of Patients With and Without Loop Diuretic Therapy at the Time of Neurohumoral Sampling

	No Diuretic	Diuretic	p Value
Number	27	9	
Age (yrs)	56 ± 10	62 ± 8	NS
Male (%)	93	89	NS
Killip class >1	37	89	<0.05
Radionuclide ventriculography-LV ejection fraction (%)	32 ± 3	25 ± 7	<0.02
End-diastolic volume (ml)	224 ± 2	255 ± 45	NS
End-systolic volume (ml)	128 ± 37	167 ± 41	<0.02
Akinesia and dyskinesia (%)	22 ± 10	32 ± 10	<0.02
LV aneurysm (%)	44	78	NS
Pulmonary artery mean (mm Hg)	6 ± 2	7 ± 2	NS
Pulmonary artery wedge mean (mm Hg)	12 ± 5	17 ± 7	<0.05
LV diastolic (mm Hg)	20 ± 7	24 ± 7	NS
Arterial mean (mm Hg)	79 ± 8	81 ± 12	NS
Cardiac index (liter/min/m ²)	2.8 ± 0.8	2.4 ± 0.7	NS
Norepinephrine (pg/ml)	250 ± 117	336 ± 277	NS
Angiotensin II (pg/ml)	24 ± 9	48 ± 35	<0.002
Plasma renin activity (ng/ml/hour)	1.9 ± 19	4.9 ± 2.9	<0.0001
Aldosterone (ng%)	13 ± 15	34 ± 24	<0.005
Serum sodium	140 ± 3	136 ± 3	<0.002

Values are expressed as mean ± standard deviation where applicable.
LV = left ventricular; NS = not significant.

cent akinesia and dyskinesia ≥ 30 . Right-sided cardiac filling pressures were normal while left-sided cardiac filling pressures were slightly increased (Table I).

Diuretics were administered much more frequently to study patients with a Killip classification >1 (Table II). Patients taking diuretics also had a lower mean ejection fraction, a higher end-systolic volume, more extensive wall motion abnormalities, and a higher mean pulmonary arterial wedge pressure than their counterparts not receiving diuretics. Patients taking diuretics had significantly increased levels of aldosterone II, plasma renin activity and aldosterone when compared with the 27 study patients not receiving diuretics. In this group of 36 patients, plasma levels of angiotensin II ($p < 0.01$), renin ($p < 0.01$) and aldosterone ($p < 0.05$) were found to correlate with Killip classification. Elevated plasma renin activity also correlated with the extent of wall motion abnormality (percent akinesia and dyskinesia) ($p < 0.05$) and the presence of LV aneurysm ($p < 0.005$). The administration of β blockers correlated with decreased plasma levels of angiotensin II ($p < 0.05$), renin ($p < 0.005$) and aldosterone ($p = 0.057$). Plasma catecholamine levels did not correlate with any of these clinical parameters or with the administration of diuretics or β -adrenergic blocking agents.

The clinical, hemodynamic and morphologic variables listed in Table II were used to identify correlates of neurohumoral activation in the subset of study patients not taking diuretics. None of the variables correlated with plasma catecholamine levels in these patients. However, plasma angiotensin II levels were found to correspond with the presence of LV aneurysm ($p < 0.05$), the extent of wall motion abnormality (percent

akinesia and dyskinesia) ($p < 0.01$), the radionuclide ventriculography-LV ejection fraction ($p < 0.05$) and Killip classification ($p < 0.05$) (Figure 1). Three of these 4 variables also correlated with plasma renin activity, including the radionuclide ventriculography-LV ejection fraction ($p < 0.01$), the percent akinesia and dyskinesia ($p < 0.05$) and the presence of LV aneurysm ($p < 0.05$); only the percent akinesia and dyskinesia correlated with plasma aldosterone levels ($p < 0.05$).

Plasma atrial natriuretic peptide and vasopressin levels were determined in unselected subgroups of the study population. Plasma atrial natriuretic peptide levels, measured in 13 subjects, were generally elevated (105 ± 54 pg/ml, range 26 to 219), with normal values defined as 10 to 40 pg/ml. In contrast, plasma vasopressin levels, measured in 17 subjects, were consistently within normal limits and averaged 0.6 ± 0.4 pg/ml (range 0.3 to 1.3 [normal 1 to 3]). Only 2 of the 13 patients in whom plasma atrial natriuretic peptide was determined and 1 of the 17 in whom vasopressin was measured were taking diuretics at the time of the study.

DISCUSSION

Neurohumoral activation is a characteristic finding in patients with severe chronic CHF.^{1,2,5,6} Stimuli to neurohumoral activation include hemodynamic abnormalities, baroreceptor dysfunction, a variety of clinical

parameters and concomitant drug therapy.¹⁹⁻²⁰ Although neurohumoral activation appears to be a homeostatic response, it may play a deleterious role in the progression of CHF.^{1,2,7} By focusing on asymptomatic patients with LV dysfunction, it may be possible to identify pathophysiologic correlates of neurohumoral activity in the absence of overt CHF.

This study was designed to examine a relatively homogeneous population of patients in the recovery phase of a first acute MI with LV ejection fraction $\leq 45\%$. Furthermore, only patients without clinically overt CHF were enrolled. Our findings demonstrate that neurohumoral activation can be identified in asymptomatic patients within 1 month of acute MI. As expected, the most powerful predictor of neurohumoral activation is the administration of loop diuretics. Patients taking loop diuretics had significantly increased levels of plasma renin activity, angiotensin II and aldosterone. Patients taking diuretics had larger infarctions and more clinical evidence of LV dysfunction than their counterparts not taking diuretics. Furthermore, the administration of diuretics has been reported to activate the renin-angiotensin system in normal subjects, as well as in patients with mild CHF.^{21,22}

In the subgroup of patients not receiving diuretics, we have identified 4 parameters that correlate with the presence of increased plasma neurohumoral activity in

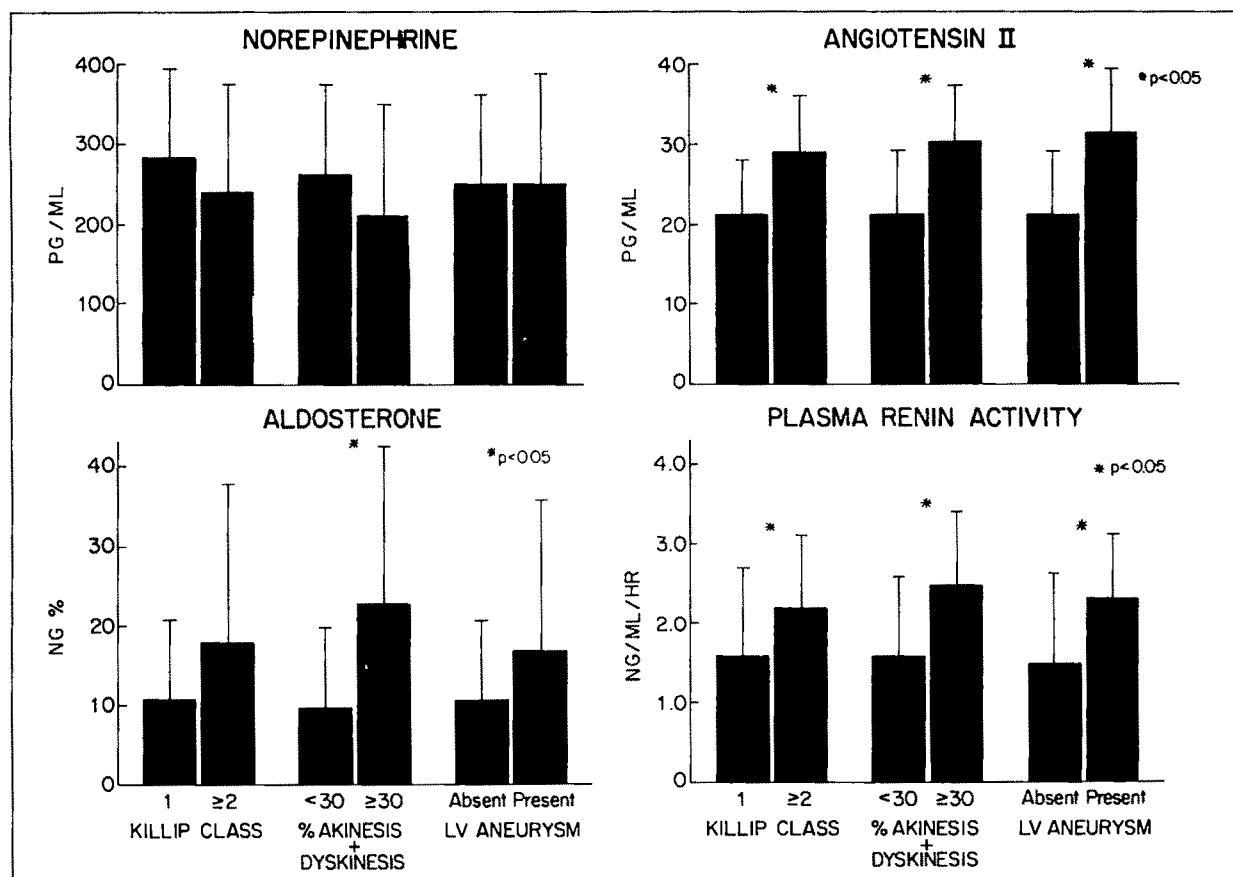


FIGURE 1. Plasma neurohumoral levels in the 36 study patients not taking diuretics. Comparisons were made for each of the neurohormones shown in relation to the dichotomized clinical or angiographic variables listed on the horizontal axis. Statistically significant differences were defined as $p < 0.05$ and are indicated by the superimposed asterisk. Mean values \pm standard deviation are shown. LV = left ventricular.

the absence of any identifiable hemodynamic abnormality. These parameters include Killip classification, extent of LV wall motion abnormality, the radionuclide ventriculography-LV ejection fraction and the presence of an aneurysm in the left ventricle. The Killip classification of patients was based on clinical findings made within 72 hours of hospitalization for acute MI, and this apparent correlation leads to the suggestion that patients with transient clinical pulmonary congestion have a persistent, although unidentified, stimulus for increased neurohumoral activity. The consistent association of the remaining related parameters (i.e., percent akinesia and dyskinesia, LV ejection fraction and LV aneurysm) with increased plasma renin activity and angiotensin II levels suggests that LV dysfunction may promote neurohumoral activation in the absence of clinically apparent CHF.

Plasma atrial natriuretic peptide levels were generally elevated. The stimulus for the release of this hormone is unclear but this finding suggests that the mild observed increase in LV filling pressure was of biologic significance. The small number of patients in whom this parameter was measured precluded further analysis in this data set. Interestingly, however, atrial natriuretic peptide has been reported to increase in rats after experimental acute MI²³ in proportion to the extent of LV dysfunction. Furthermore, a recent study also described a potential role for myocardial dysfunction alone in provoking increased plasma levels of atrial natriuretic peptide.²⁴ Because the patients included in this study were, by definition, hemodynamically well compensated, the current findings of increased plasma atrial natriuretic peptide levels appear to confirm these prior observations.

Elevations in vasopressin and norepinephrine were not identified in our patients. This finding is consistent with previous reports that these 2 neurohormones tend to be elevated in patients with more severe CHF.⁷ All of the patients included in this study were free of clinical symptoms of CHF, and, accordingly, elevations in norepinephrine or vasopressin, or both, would not be expected in this group. Other investigators have described increased serum catecholamine levels in patients within 72 hours of acute MI, particularly in patients with acute MI complicated by CHF.⁸ Those patients clearly differ from those described in this study, who were studied an average of 19 days after infarction.

Selective neurohumoral activation can be identified in hemodynamically compensated patients during the recovery phase of an anterior wall acute MI and appears to be related to the extent of LV dysfunction. Elevated levels of neurohormones, particularly angiotensin II, may potentially play a role in the pathologic sequence of ventricular hypertrophy²⁵ and dilatation²⁶ after acute MI. The role of neurohumoral activation in promoting the transition from asymptomatic LV dysfunction to overt CHF merits further investigation.

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Prevalence, Incidence and Prognosis of Recognized and Unrecognized Myocardial Infarction in Persons Aged 75 Years or Older: The Bronx Aging Study

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The prevalence, incidence and prognosis of recognized and unrecognized Q-wave myocardial infarction (MI) was assessed in an 8-year prospective study of 390 community-based subjects (age 75 to 85 years at entry, mean 79 years). Subjects were studied at baseline and with annual follow-up electrocardiographic (ECG) exams. At baseline, 7.9% had a history of MI without ECG evidence, 6.4% had ECG evidence of Q-wave MI without clinical history, 4.1% had both clinical history and ECG evidence and 81.5% had neither history nor ECG evidence (control subjects). After an average follow-up period of 76.2 months, the total mortality rate was 5.9/100 person-years for subjects with some evidence of MI at baseline versus 3.9 in the control group ($p = 0.059$). The incidence of cardiovascular disease in subjects with evidence of MI was 8.8/100 person-years versus 4.7 among control subjects ($p = 0.002$). During the follow-up period, 115 new Q-wave MIs occurred (50 unrecognized, rate 2.4/100; 65 recognized, rate 3.2/100). There was no difference in mortality and morbidity outcome between subjects with recognized and unrecognized MIs. Those with only a history of MI at baseline had a threefold greater risk of a new MI (recognized and unrecognized) than the control group ($p = 0.003$).

Unrecognized Q-wave MI is a common occurrence in the "old old" with subsequent morbidity and mortality prognosis comparable to that of recognized MI. History of MI alone in this age group is also associated with an increased risk of MI, suggesting the need for better diagnostic markers of myocardial ischemia in the old.

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The population of the United States is aging, and the numbers and proportion of persons >75 years of age ("old old") are steadily increasing. In 1987, there were almost 30 million persons >65, 41% (12.2 million) of whom were ≥ 75 ,¹ and by the year 2000 this figure will approach 50%.² With the advent of an aging elderly population, the health professional is obliged, now more than ever, to deal with the health and illness of the old old.

Coronary artery disease accounts for a high proportion of morbidity and mortality in old age. Myocardial infarction (MI) in the elderly often has an atypical presentation, with the classic description of retrosternal chest pressure or tightness often absent. Atypical symptoms of MI can include nausea and vomiting, dyspnea or mental status alterations. It is not uncommon for elderly patients to dismiss these atypical symptoms or not have detectable symptoms at all, and therefore not seek medical attention.

Asymptomatic or atypical MIs have been recognized for years. Initially, the prevalence of these events was thought to be quite low,³ <10% of all MIs. In recent epidemiologic studies, however, the prevalence of unrecognized MI has been found to be between 25 and 30%.⁴⁻⁶ Most of these studies examined middle-aged populations (age on entry ≤ 65), and except for the Framingham study,⁴ have only examined men.

This is a report on the prevalence, incidence and prognosis of recognized and unrecognized MI in a cohort of old old individuals who have been followed prospectively for up to 8 years as part of the Bronx Aging Study. For the purposes of this study, unrecognized MI is defined as either a completely painless MI or an MI presenting atypically, and thus not recognized until a routine serial electrocardiogram is performed.

METHODS

The Bronx Aging Study, which began in 1980, is a prospective study of cardiovascular disease and dementia in the old old. The inception cohort was 488 volunteer subjects (75 to 85 years at entry). Subjects were recruited from areas in and around the borough of the Bronx, New York. At baseline, all subjects were functioning normally in their daily activities, and did not meet the criteria for dementia as set forth in the Diagnostic and Statistical Manual of the American Psychiatric Association.⁷ Furthermore, none of the subjects

TABLE I Study Subjects by Myocardial Infarction Status			
	No. (%)	History	Q-wave MI by ECG
Group 1 (history only)	31 (7.9)	+	0
Group 2 (ECG only)	25 (6.4)	0	+
Group 3 (history and ECG)	16 (4.1)	+	+
Group 4 (control)	318 (81.5)	0	0

ECG = electrocardiogram; M = myocardial infarction.

had a known terminal disease. Subjects understood the longitudinal nature of the study, gave informed consent and agreed to return for annual evaluations. Intake occurred over a 2.5-year period. The average subject age at intake was 79 years, and 35.5% were men, while 64.5% were women. The cohort was predominantly Caucasian (90%).

The initial evaluation included physical examination, complete medical history, psychosocial history and questionnaires, family history, current and past medications, resting electrocardiogram, 24-hour ambulatory electrocardiographic (ECG) monitoring, complete blood and biochemical screens and neuropsychological evaluations.

Subjects returned annually for a complete reevaluation; the average time to reexamination was 15 months. In addition, hospital records and death certificates were obtained from those subjects who had experienced intervening morbidity and mortality. All subjects received annual electrocardiograms, which were read by an independent cardiologist. Three hundred ninety subjects returned for at least 1 repeat evaluation, and this report is based on that cohort. All electrocardiograms were used for identification of a new event after baseline.

A diagnosis of MI was made when either an electrocardiogram showed a pattern that included pathologic Q waves with a duration of ≥ 0.04 seconds, or loss of initial R waves, or a clinical history was obtained from a combination of patient history and hospital records. An

unrecognized MI was said to have occurred when there was ECG evidence of a Q-wave MI without a corresponding clinical history. It was not possible from our data to distinguish a completely silent MI from an atypical symptomatic MI, and both were considered to be unrecognized. Subjects with left bundle branch patterns or paced rhythms that precluded a diagnosis of MI were grouped with subjects who lacked ECG evidence of MI.

Incidence rates (per 100 person years) were calculated on the basis of weighted average exposure time. Differences between rates were compared using tests of 2 proportions. As in Table I, subjects were divided into 4 groups based on their entry MI status. Group 1 (history) were those subjects with a clinical history of MI without accompanying ECG evidence of Q-wave MI. Group 2 (electrocardiogram only) were those subjects with evidence of Q-wave MI on baseline electrocardiogram but without supporting clinical history of MI. Group 3 (history and electrocardiogram) were those subjects with both clinical history and ECG evidence of Q-wave MI. Group 4 were those subjects with neither clinical history nor ECG evidence of MI. Subjects in this last group served as control subject for this analysis.

Selected health and demographic characteristics of the 4 groups at baseline were essentially the same (Table II). Additionally, at study entry, 67% were receiving some type of cardiovascular drug alone or in combination, 45% were receiving diuretics, 13% were receiving digoxin and 10% were receiving oral β -adrenergic blockers. No subjects were receiving calcium-channel blockers on entry. Only 6% of the subjects were not receiving any medication.

RESULTS

Unrecognized myocardial infarction: At entry, 25 subjects (6.4%) had evidence of unrecognized MI by electrocardiogram. Thus, of the 72 subjects with history and ECG evidence of MI at baseline, 34.7% were unrecognized. During the 8 years of follow-up (range 5 to 8 years), there were an additional 50 unrecognized MIs

TABLE II Selected Health and Demographic Characteristics by Baseline Myocardial Infarction Status					
Characteristic (mean \pm SD)	Group 1 History (n = 31)	Group 2 ECG Only (n = 25)	Group 3 History and ECG (n = 16)	Group 4 Control (n = 318)	Overall Sample (n = 390)
Age (yrs)	79 \pm 3	80 \pm 4	78 \pm 3	79 \pm 3	79 \pm 3
Total cholesterol (mg/dl)	235 \pm 45	225 \pm 54	214 \pm 39	225 \pm 44	225 \pm 42
Hypertension (%)	45	32	44	52	50
Female (%)	55	60	50	64	64
Diabetes mellitus (%)	25	10	19	11	12
Cigarette smoker (%)	50	35	25	37	37
Diuretics (%)	58	44	44	43	45
β -blockers (%)	42	4	31	6	10
Digoxin (%)	29	20	25	10	13
No medication (%)	0	4	0	7	6

ECG = electrocardiogram; SD = standard deviation.

TABLE III Cardiovascular Morbidity and Mortality by Myocardial Infarction Subgroup

Group	Rate/100 Person Years	p Value*
1 (History only)	9.5	0.009
2 (ECG only)	7.4	NS
3 (ECG and history)	9.5	0.053
1,2,3 (Combined)	8.8	0.002
4 (Control)	4.7	

* Control versus other groups.
ECG = electrocardiogram; NS = not significant.

(2.4/100 person-years) and 65 recognized MIs (3.2/100 person-years). Because of the limitation in our coding of electrocardiograms, only subjects without any prior ECG evidence of MI (groups 1 and 4) could be classified for a new, unrecognized MI. Therefore, groups 2 and 3 were not included in this analysis. (There were 3 new clinical MIs in group 2 [rate = 3.6/100 person-years] and 5 new clinical MIs in group 3 [rate = 3.7/100 person-years]).

Subjects in group 1 had 11 new unrecognized MIs (7.2/100) and 12 new recognized MIs (7.1/100). Group 4 (control) subsequently developed 39 unrecognized MIs (2.1/100) and 53 new recognized MIs (2.4/100, Figure 1). Thus, the rate of subsequently unrecognized MIs was essentially the same as that of recognized MIs, and those with a prior history of MI were 3

TABLE IV Total Mortality by Myocardial Infarction Subgroup

Group	Rate/100 Person-Years	p Value*
1 (History)	3.9	NS
2 (ECG only)	7.1	0.03
3 (ECG and history)	8.4	0.059
1,2,3 (Combined)	5.9	0.059
4 (Control)	3.9	

* Control versus other groups.
ECG = electrocardiogram; NS = not significant.

times more likely to develop a subsequent MI (either recognized or unrecognized) than those subjects without any prior indications of MI ($p = 0.0001$).

Total cardiovascular morbidity and mortality: All clinical events were classified as either cardiovascular or non-cardiovascular. Cardiovascular events included MI (fatal, non-fatal and unrecognized), cerebrovascular (fatal, non-fatal and transient ischemic attacks) and other heart deaths (i.e., congestive heart failure) (Table III).

Subjects in group 1 developed cardiovascular disease at a rate of 9.5/100 person-years, compared to 7.4/100 (group 2), 9.5/100 (group 3) and 4.7/100 (group 4). Subjects in group 1 (history) and group 3 (history and electrocardiogram) had a significantly higher rate of cardiovascular disease when compared to control subjects ($p = 0.009$ and 0.053 , respectively).

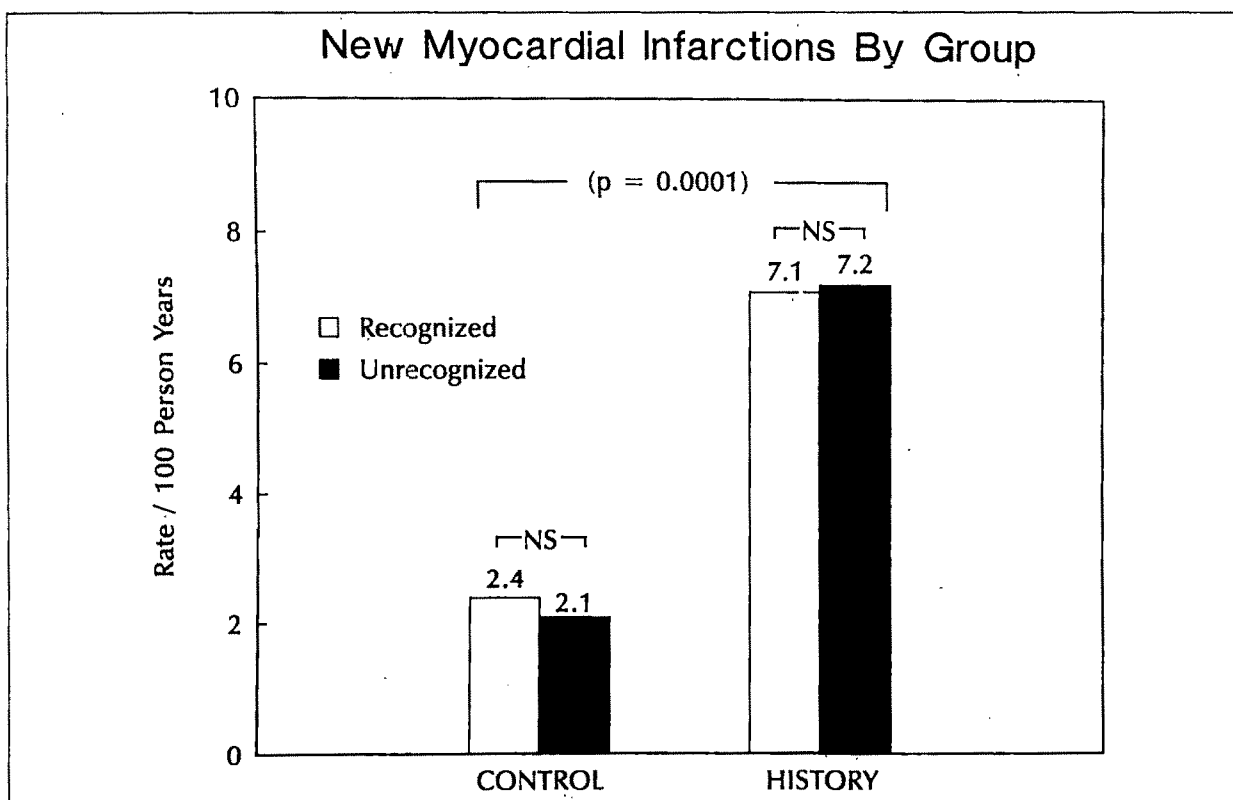


FIGURE 1. Rate of new myocardial infarction (MI, recognized and unrecognized) in Bronx Longitudinal Aging Study. Control = subjects with no evidence of MI by history or electrocardiogram at baseline; History = subjects with clinical history of MI at baseline with no electrocardiographic evidence of Q-wave MI present; NS = not significant.

TABLE V Previous Reports of Unrecognized Myocardial Infarctions

Study and Year	No. Pts.	Sex M/F	Age (yrs)	% Unrecognized MI	Type of Study
Roseman (1954) ³	220*	163/57	no limit	4.5	Autopsy and ECG chart review
Rodstein (1956) ¹¹	700	both	≥60	31 silent 41 atypical	Chart review over 4 years
Johnson et al (1959) ⁸	143	105/38	no limit	50	Autopsy
Lindberg et al (1960) ⁹	756	all male	50-59	15	Prospective study with 4-year follow-up
Rosenman et al (1967) ¹⁰	3,182	all male	39-59	30	Prospective study with 4.5-year follow-up
Medalie et al (1976) ⁵	9,509	all male	≥40	39.8 overall 2.0/1000 pt yrs 40-49 10.6/1000 pt yrs 60+	Prospective study with 7-year follow-up
Kannel et al (1984) ⁴	5,127	both	30-62 at entry	30 overall <75 (28%) ≥75 (39.7%)	Prospective study with 30-year follow-up
Grimm et al (1987) ⁶	2,132	all male	35-57	25.4	Prospective study
Yano et al (1989) ¹²	7,331	all male	45-68 at entry	33	Prospective study with 6-year follow-up

* Definite MIs.
Abbreviations as in Table I.

Overall, subjects with any evidence of MI at study entry (groups 1, 2 and 3) had a higher incidence of cardiovascular disease (8.8/100 person-years) when compared to control subjects (4.7/100, $p = 0.002$).

Total mortality: During an average follow-up of 76.2 months (range 5 to 8 years), 106 people died (Table IV). Those subjects with some evidence of MI at baseline (groups 1, 2 and 3) had a total mortality rate of 5.9/100 person-years, whereas group 4 (control subjects) had a rate of 3.9/100 ($p = 0.059$).

Compared to control subjects, the mortality rate of subjects in group 1 (history) was 3.9/100 person-years (difference not significant); that of group 2 was 8.4/100 ($p = 0.03$), and that of group 3 was 7.1/100 ($p = 0.059$). There were no significant differences in outcome between groups 1, 2 and 3. Thus, the prognosis for subjects entering with an unrecognized MI was similar to those with a clinical MI.

DISCUSSION

Reports of coronary thrombosis without pain have been described as far back as 1912, and unrecognized MI is now a well documented clinical entity.³ Estimates of the proportion of unrecognized MI have ranged from 0 to 61%. The earliest studies were predominantly autopsy studies, with an incomplete retrospective review of clinical history. Roseman,³ in a retrospective case study of 220 patients with MI, reported a 4.5% proportion of completely painless MIs, with an additional 6.8% proportion having atypical symptoms. He concluded that

silent MI did exist but its rate of occurrence was extremely low.

In more recent studies (Table V), many of them prospective in design, the proportion of unrecognized MI has averaged 30%.^{3-6,8-12} Our findings at baseline of a 34.7% proportion of MIs that were unrecognized is comparable to these recent studies. In our study, the incidence of recognized MI was 3.2/100 person-years, and unrecognized 2.4/100, with the unrecognized MIs accounting for 43.7% of the total. Studies from Framingham⁴ and Israel⁵ also found the proportion of unrecognized MIs to increase with advancing age.

There are a number of theories proposed to explain why silent or painless MIs occur in the elderly. Some investigators have suggested a defective myocardial ischemia and infarction warning system.¹³ Marked ECG ST-segment depressions on exercise tests without accompanying pain are not uncommon findings in patients with significant coronary artery disease. Sensory neuropathy or an increased pain threshold have been suggested as mechanisms to explain silent myocardial ischemia.¹⁴

Rodstein¹¹ prospectively followed a group of ambulatory nursing home patients >60 years for 5 years, and found 31% of all non-fatal MIs to be silent, and 41% atypical in presentation with symptoms such as dyspnea, dizziness, vertigo, cough, nausea or abdominal pain as the predominant complaint. He also found that these atypical presentations were more common in patients with hypertension and severe mental deteriora-

tion. Other investigators have found that atypical MI presentations in the elderly were associated with an impaired mental score.¹⁵ The classic triad of chest pain, ECG changes and elevated cardiac enzymes were reported by 1 group to occur in only a minority of elderly patients presenting with acute MI, and confusion, vomiting, syncope and shortness of breath were reported to be more likely to be the presenting complaints.¹⁶ Our findings from the Bronx Aging Study confirm these earlier observations that elderly patients are likely to have unrecognized MIs.

Our findings also confirm those of previous prospective studies,^{4,6,10,12} which found that silent MIs were just as likely as clinical MIs to be associated with increased rates of cardiovascular morbidity and total mortality.

Another interesting finding in the Bronx Longitudinal Aging Study was the high proportion of subjects having a history of MI but without confirmatory ECG evidence at baseline. It is well known that ECG evidence of a Q-wave MI can disappear.¹⁷⁻²⁰ Usually this occurs within the first 2 to 3 months after the infarction,¹⁸⁻²⁰ and various studies have reported an incidence of this phenomenon to be between 14 and 48%.¹⁸⁻²⁰ We found that 43% of our subjects (with some evidence of past MI) gave a clinical history at baseline of MI but lacked ECG evidence of Q-wave MI; part of this group had non-Q-wave MI and others lacked any ECG evidence altogether. Yet, interestingly, their mortality was similar to that of control subjects, although they had the highest incidence of new cardiovascular morbidity, with a threefold greater risk of unrecognized MIs than control subjects.

In the Bronx Aging Study, unrecognized MIs were defined only by the presence of Q waves on the electrocardiogram. Therefore, non-Q-wave MIs were missed, and the true incidence of unrecognized MIs may be higher. In addition, a specifically detailed history looking for atypical symptoms was not obtained. Thus, we were unable to differentiate truly painless MIs from atypical MIs. Another limitation in our study was the coding of electrocardiograms. We did not localize the site of the infarction, nor did we code for subsequent

new MIs by electrocardiogram, causing us to underestimate the true incidence of unrecognized MIs.

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Randomized Controlled Trial of Late In-Hospital Angiography and Angioplasty Versus Conservative Management After Treatment with Recombinant Tissue-Type Plasminogen Activator in Acute Myocardial Infarction

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Although both the European Cooperative Study Group and the Thrombolysis in Myocardial Infarction IIB trial indicated that angiography and angioplasty as routine measures after thrombolytic treatment do not improve clinical outcome in patients with acute myocardial infarction, the potential benefit of angioplasty may have been negated by the fact that the procedure was performed too soon (<32 hours) after admission. A similar study was designed in which delayed invasive treatment was compared with conservative treatment in 201 patients with acute myocardial infarction given recombinant tissue-type plasminogen activator. The 97 patients randomized to the invasive group underwent routine coronary angiography and angioplasty 5 ± 2 days after thrombolytic therapy, whereas the 104 patients randomized to the conservative group underwent angiography only for recurrent postinfarction angina or exercise-induced ischemia. Baseline characteristics of both groups were similar. In the invasive group, 92 patients underwent angiography, 49 angioplasty and 11 coronary artery bypass surgery. In the conservative group, 40 patients experienced early ischemia, 39 underwent angiography, 20 angioplasty and 4 coronary artery bypass surgery. Reinfarction rate and preservation of left ventricular function at discharge or 8 weeks after discharge did not differ in the 2 groups. Total mortality after a mean follow-up of 10 months was 8 of 97 in the invasive and 4 of 104 in the conservative groups ($p = 0.15$). However, if only patients who died after the timing of the scheduled protocol catheterization in the invasive arm were included, mortality was 5 of 94 and 0 of 100 in the invasive and conservative treatment

groups, respectively ($p = 0.02$). A significantly higher rate of rehospitalization was observed among patients assigned to the conservative group and in both groups, and a history of angina pectoris was significantly associated with more rehospitalizations. Results of this study indicate that conservative treatment is preferable to invasive treatment, even when cardiac catheterization is delayed. (Am J Cardiol 1990;66:538-545)

The role of angioplasty as an adjuvant to thrombolytic therapy for acute myocardial infarction (MI) has been recently reevaluated. The frequency of high-grade underlying stenosis of the infarct artery after thrombolysis¹ combined with the high incidence of early reocclusion (up to 20% in some series²), has led to the seemingly logical combination of thrombolysis followed by prophylactic angioplasty.³ To determine the optimal timing of the prophylactic treatment, 2 studies compared immediate versus delayed coronary angioplasty.^{4,5} These studies indicated that immediate mechanical revascularization offered no benefit and was accompanied by higher reocclusion rates, and possibly by increased mortality.

The question of whether angioplasty benefits patients without evidence of myocardial ischemia in the acute and subacute phase of acute MI initiated the European Cooperative Study Group (ECSG) and the Thrombolysis in Myocardial Infarction (TIMI) IIB, trials that compared invasive and conservative treatment strategies after thrombolytic therapy.^{6,7} Both studies showed that routine invasive treatment involving coronary angiography and angioplasty had no advantage over conservative treatment; the mortalities associated with both treatments were similar. However, in both studies, the potential benefit of angioplasty may have been masked by the fact that the procedure was performed too soon (<32 hours) after the acute coronary event, at a time when the risk of reocclusion is still high.⁸

Our study was designed to compare delayed (≥72 hours) invasive treatment to conservative treatment in

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which invasive work was done only when indicated by clinical signs of myocardium at risk. Patients with evolving acute MI treated with recombinant tissue plasminogen activator (rt-PA) were thus randomized to undergo late in-hospital coronary angiography and angioplasty or to undergo conservative treatment with selective angiography only when indicated by objective evidence of myocardial ischemia. Our results indicate that after thrombolytic therapy, routine delayed coronary angiography does not improve short- and long-term outcome when compared with selective intervention in patients with evidence of myocardium at risk.

METHODS

Patients: Patients were enrolled in the study by way of the emergency ward and mobile intensive care units. The study protocol was approved by institutional committees on human research and all participating patients gave their informed consent.

The entry criteria were as follows: age <73 years, severe chest pain >30 minutes but no longer than 4 hours; ST-segment elevation of 0.1 mV in ≥ 2 contiguous electrocardiographic leads, no left bundle branch block on the qualifying entry electrocardiogram, no history of congestive heart failure or cardiac surgery, diastolic blood pressure <120 mm Hg, no history of terminal illness and no bleeding predisposition (i.e., oral anti-coagulant therapy, recent trauma, past bleeding history, or cerebrovascular accident during the last 6 months). Patients with cardiogenic shock were not excluded.

Thrombolytic regimen: A total dose of 120 mg rt-PA (G11035, supplied by Boehringer-Ingelheim, West Germany) was given during a 6-hour infusion that consisted of a 10-mg bolus followed by a continuous infusion of 50 mg in the first hour, 20 mg in the second hour, and 10 mg during each of the following 4 hours.

Concomitantly, heparin was infused in a bolus of 5,000 IU and then continued at 25,000 IU/24 hours. The dose was adjusted to keep the activated partial thromboplastin time between 1.5 to 2 times the baseline. Heparin infusion was continued for ≥ 5 days except in the following 3 instances: patients who underwent a successful coronary angioplasty, in whom heparin was discontinued after 24 hours; cases of bleeding; and patients referred to urgent (before discharge) coronary bypass surgery, in whom heparin was continued until surgery. Aspirin (250 mg/day) was administered after the first 24 hours and continued during follow-up. Conventional antianginal and anticongestive therapy was used as needed. All patients were treated prophylactically with 2 g of intravenous lidocaine in the first 24 hours.

Randomization: Patients were randomized to invasive or conservative treatment groups on the basis of alternating 2-month periods (Table I). Thus, all patients enrolled during a 2-month "invasive" period were assigned to the invasive group, whereas all patients enrolled during a "conservative" 2-month period were assigned to the conservative group. This randomization method was chosen because patient-by-patient randomization would have been difficult, especially since a significant number of patients were enrolled by way of mobile coronary care units. Patients enrolled through the

TABLE I Enrollment in the Invasive and Conservative Treatment Groups by Month

	Invasive Treatment	Conservative Treatment
December 1987	5	3
January–February 1988	—	29
March–April 1988	33	—
May–June 1988	—	27
July–August 1988	27	—
September–October 1988	—	27
November–December 1988	32	—
January 1989	—	8
Total	97	104

emergency ward were treated as soon as possible after admission, with rt-PA infusion initiated either in the emergency room or on admission to the intensive coronary care unit. In all patients in the invasive group, coronary angiography was performed >72 hours after admission. Patients in the conservative treatment group received conventional care; coronary angiography was performed only if postinfarction angina or hemodynamic instability occurred during hospitalization or if severe ischemia was provoked during a predischarge exercise test.

Criteria for percutaneous transluminal coronary angioplasty: Patency of the coronary arteries was evaluated at the laboratory of each medical center and by a consensus reading of all angiograms by the same 2 coronary angiographers who were blinded to the clinical course of the patients except for the electrocardiographic localization of the infarction. Severity of coronary artery disease was determined by visual assessment of the reduction in luminal diameter (% stenosis) and TIMI⁹ gradings of perfusion for each coronary artery and its major branches.

Patients in both the invasive and conservative groups found to have >50% reduction in the luminal diameter of the infarct-related artery underwent an ad hoc percutaneous transluminal coronary angioplasty unless the infarct artery was considered insignificant, the lesion was considered not suitable for angioplasty for other reasons, or the patient was referred to coronary bypass surgery because of 3-vessel coronary artery disease, left main or left main equivalent disease. Thus, once coronary angiography was performed, the decision to proceed with angioplasty was solely based on coronary anatomy (suitable lesion in the infarct artery) and not on the patient's clinical condition. The angioplasty was defined as successful when blood flow was normal or improved according to the TIMI criteria⁵ and both an absolute reduction in luminal stenosis by >20% and final luminal narrowing of <60% were achieved.⁷

Measurement of left ventricular function: During the hospitalization, each patient underwent 2 radionuclide studies to assess left ventricular function, the first as soon as possible after admission but not later than 60 hours (mean time 1.2 ± 0.8 days) and the second at discharge. All radionuclide examinations and left ventricular ejection fraction were assessed by the same 2 experienced cardiologists, who were blinded to the clinical course of the examined patients.

TABLE II Baseline Characteristics of Patients in the Invasive and Conservative Treatment Groups

	Treatment		p Value
	Invasive (n = 97)	Conservative (n = 104)	
Mean age (yrs \pm SD)	58 \pm 9	57 \pm 9	
Men (%)	85	84	
High-risk patients (% of patients)	68	68	
Anterior infarction	48	57	0.3
Previous infarction	25	18	0.34
Rales $>1/3$ lung field*	5.1%	4.8%	
Atrial fibrillation / flutter	4.1%	2.8%	
Angina pectoris			
None	54%	55%	
<6 months	33%	35%	
>6 months	12%	10%	
Admission heart rate (minutes, mean \pm SD)	77 \pm 16	77 \pm 20	
Systolic blood pressure (mm Hg, mean \pm SD)	125 \pm 27	128 \pm 26	
Time to treatment (hours, mean \pm SD)	2.0 \pm 0.8	2.0 \pm 0.8	

* 3.0 and 2.8% of the patients in the invasive and conservative treatment groups, respectively, were admitted with Killip grade IV.
SD = standard deviation.

TABLE III In-Hospital Complications

	Treatment		p Value
	Invasive (n = 97)	Conservative (n = 104)	
All Patients			
In-hospital reinfarction	15 (16)	10 (10)	0.15
In-hospital ischemia	13 (13)	16 (15)	
Emergency procedures	15 (15)	13 (12)	
Re-PTCA	3 (3)	3 (3)	
Emergency CABG	4 (4)	0 (0)	0.52
Other procedures*	8 (8)	10 (10)	
Bleeding complications	11 (11)	9 (9)	0.34
Local hematoma	2 (2)	4 (4)	
Macroscopic hematuria	2 (2)	2 (2)	
Gastrointestinal bleeding	6 (6)	3 (3)	
Retroperitoneal bleeding	1 (1)	0 (0)	
Intracranial bleeding	0 (0)	1 (1)	
Blood transfusion	3 (3)	0 (0)	
Congestive heart failure	9 (9)	4 (4)	
Mortality at discharge	5 (5)	4 (4)	
Total patients with complications	34 (35)	28 (27)	
Patients with increased risk	n = 66	n = 71	
In-hospital reinfarction	10 (15)	6 (8)	0.17
Emergency procedures†	6 (9)	8 (11)	
Bleeding complications	7 (11)	6 (8)	
Congestive heart failure at discharge	8 (12)	4 (6)	0.15
Mortality	4 (4)	4 (6)	
Total patients with complications	24 (36)	19 (27)	0.15
Patients without increased risk	n = 31	n = 33	
In-hospital reinfarction	5 (16)	4 (12)	
Emergency procedure†	9 (29)	5 (15)	0.15
Bleeding complications	4 (12)	3 (10)	
Congestive heart failure at discharge	1 (3)	0 (0)	
Mortality	1 (3)	0 (0)	
Total patients with complications	10 (32)	9 (27)	

CABG = coronary artery bypass surgery; PTCA = percutaneous transluminal coronary angioplasty.

* Electroconversion, pacemaker insertion, cardiopulmonary resuscitation.

† Coronary angioplasty, bypass operation, electroconversion, pacemaker insertion, cardiopulmonary resuscitation.

Effort-tolerance test: A modified Bruce effort-tolerance test was performed in all patients in the conservative group between the seventh and the tenth day of hospitalization except in patients who were unstable early during their hospitalization and underwent coronary angiography before discharge. The effort-tolerance test was performed targeting a heart rate of 120 beats/min. When the patient could not reach a heart rate of 120 beats/min, but had no evidence of myocardial ischemia, the test was defined as inconclusive and the patient was treated as if the test had been negative. A test was defined as positive when ≥ 1 of the following occurred: typical ischemic chest pain, ≥ 2 mm ST depression 0.08 second after the J point, or a decrease of 15 mm Hg in blood pressure from baseline level.

Patient evaluation and follow-up: All patients stayed in the coronary care unit ≥ 24 hours. The diagnosis of MI was confirmed by either an increase of creatine kinase MB fraction $>5\%$ or appearance of a new Q wave not present on the initial electrocardiogram.

After discharge, patients had follow-up clinic visits at 2, 6 and 12 months. No patient was lost to follow-up. During the clinic visit at 2 months, each patient underwent a symptom-limited effort-tolerance test and exer-

cise radionuclide ventriculography. During the 6- and 12-month clinic visits, only the symptom-limited effort tolerance test was performed.

Evaluation of patients with increased risk: Patients with increased risk were defined as those with ≥ 1 of the following 6 characteristics at admission: ST-segment elevation in the precordial leads, history of previous acute MI, Killip grading ≥ 2 , systolic hypotension (<100 mm Hg) and sinus tachycardia (atrial rate >100 beats/min), atrial fibrillation or flutter, and age ≥ 70 years.

Statistical analysis of risk factors: Clinical outcome was evaluated by intention to treat for the 2 randomized groups of patients assigned to the invasive and conservative treatment groups. Univariate comparisons of the invasive and the conservative groups were done as follows: for continuous variables, by t test or by Wilcoxon rank sum test in cases of inequality of variances, expressing data as mean \pm standard deviation; for categorical variables, by chi-square test, or when relevant, by Fisher's exact test, expressing data as percentages.

On the basis of univariate analysis, the effect of relevant independent variables on the dependent variable—rate of rehospitalization—was determined by forward stepwise multivariate logistic regression analysis. The

FIGURE 1. In-hospital clinical course and treatment. CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; *including 2 patients who did not have postinfarction angina or a positive predischarge effort-tolerance test who nevertheless underwent coronary angiography followed by conservative management.

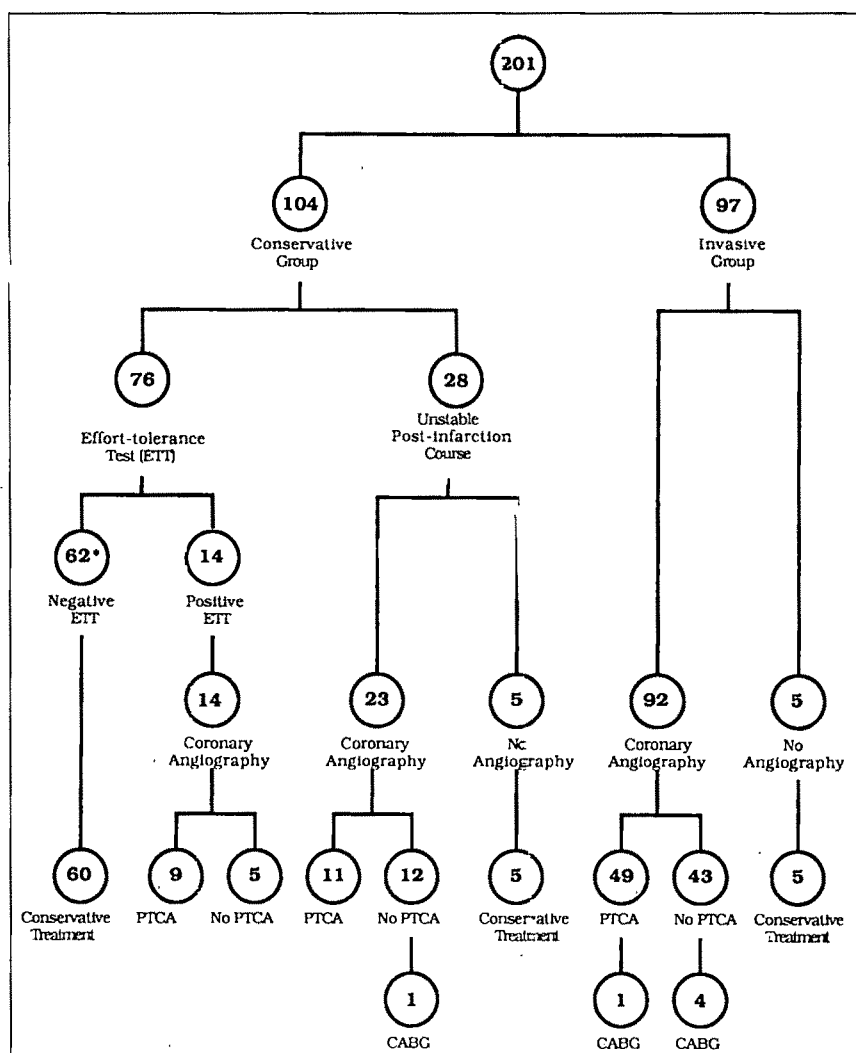


TABLE IV Ejection Fraction at Admission, Discharge and Eight Weeks in the Invasive and Conservative Groups

All Patients In-Hospital	Treatment			
	Invasive (n = 90)	EF%	Conservative (n = 104)	EF%
Immediate resting EF	(82)	48 ± 13	(94)	49 ± 13
Discharge resting EF	(89)	50 ± 15	(98)	49 ± 3
At 8 weeks				
Resting EF	(86)	51 ± 14	(89)	51 ± 11
Exercise EF—resting EF		+1.4 ± 6.5		+1.9 ± 6.5
Patients with increased risk		n = 66		n = 71
Immediate resting EF	(52)	44 ± 12	(63)	45 ± 12
Discharge resting EF	(63)	44 ± 20	(69)	44 ± 16
At 8 weeks				
Resting EF	(58)	47 ± 14	(57)	48 ± 10
Exercise EF—resting EF		+1.2 ± 6.5		+2.2 ± 6.6
Patients without increased risk		n = 31		n = 33
Immediate resting EF	(30)	56 ± 8	(31)	58 ± 12
Discharge resting EF	(31)	54 ± 16	(33)	55 ± 12
At 8 weeks				
Resting EF	(28)	59 ± 9	(32)	55 ± 9
Exercise EF—resting EF		+1.8 ± 6.6		+1.4 ± 6.1

EF = ejection fraction.

independent variables were the following: study group, age, sex, infarct location, history of angina pectoris, co-existing diabetes mellitus, decreased (<50%) left ventricular ejection fraction at discharge, and reinfarction during the hospitalization. The relative risk associated with the independent variable was derived from the logistic regression coefficient with 95% confidence limits.

RESULTS

Baseline characteristics: From December 1987 through January 1989, 201 patients with acute MI received intravenous rt-PA within 2.0 ± 0.8 hours after onset of symptoms. Ninety-seven patients were randomly allocated to the invasive treatment group and 104 patients to the conservative treatment group (Table I). The 2 populations were generally comparable (Table II); both consisted of mostly men (85%) (mean age 57 ± 9 years). The diagnosis of acute MI was confirmed in 98 and 95% of the patients in the invasive and conservative treatment groups, respectively. The percentage of patients with increased risk was practically identical in both treatment groups (68 vs 68%). Patients in the invasive group had a lower rate of first infarction in the anterior wall than patients in the conservative group (48 vs 57%). In addition, patients in the invasive group had a higher incidence of previous acute MI (25 vs 18% in the conservative group), and a higher incidence of Killip grade 4 on admission (3% in both groups), but these differences were not significant. The 2 groups did not differ with respect to prehospital duration of angina pectoris, admission heart rate, systolic blood pressure or time to treatment.

In-hospital clinical course and treatment: Of the 97 patients assigned to the invasive arm, 92 underwent rou-

tine coronary angiography 5 ± 2 days after admission (Figure 1). Coronary angiography was not performed in 5 patients because of death before 72 hours (3 patients), or unstable hemodynamic course (2 patients). No patient refused to undergo coronary angiography or angioplasty when these procedures were indicated by either the study protocol or compelling clinical reasons.

Of the 104 patients assigned to conservative treatment, 28 did not undergo an effort-tolerance test: 4 patients who died, 23 patients with early postinfarction angina and 1 patient with severe arrhythmia. Among the 76 patients who did undergo the effort-tolerance test, the results were negative in 58, inconclusive in 4 and positive in 14.

Of the 104 patients allocated to the conservative group, 39 (37%) underwent coronary angiography 11 ± 5 days after admission, 21 because of early postinfarction angina, 16 because of a positive predischarge effort-tolerance test and 2 who did not have postinfarction angina or a positive predischarge effort-tolerance test. These 2 patients did not undergo percutaneous transluminal coronary angioplasty and had an uneventful hospitalization and follow-up. For the purpose of analysis, these patients were included (by intention to treat) in the conservative group.

Coronary anatomy observed during coronary angiography was similar for the 92 patients in the invasive group and the 39 patients in the conservative group who underwent cardiac catheterization. In the invasive and conservative groups, respectively, the prevalence of infarct arteries with >50% stenosis was 84 and 92%, lesions of the left anterior descending artery were present in 42 and 44% of patients, proximal-third infarct-artery lesions were present in 44 and 51% of patients and the

severity of the infarct-artery lesion (TIMI grade 0 or 1) was 16 and 15%. The contrast left ventricular ejection fraction measured during coronary angiography was lower in the invasive treatment group than in the conservative treatment group (49 ± 25 vs 54 ± 25 , respectively, $p = 0.06$).

The rate of coronary angioplasty during hospitalization was more than double in patients assigned to the invasive group than in those assigned to the conservative group (50 vs 19%, $p < 0.01$). Angioplasty was successful 90% of the time in the invasive group (44 of 49 patients) and 95% of the time (19 of 20) in the conservative group. An additional 9 patients underwent coronary angioplasty after hospital discharge; 4 of these patients were from the invasive group and 5 from the conservative treatment group. The rate of coronary bypass operations was 3 times higher in the invasive than in the conservative group (11 of 97 vs 4 of 104, $p = 0.03$). Of these, 6 operations were performed before discharge: 5 in patients from the invasive group and 1 in a patient from the conservative group.

Complications during initial hospitalization: Mean duration of hospital stay was 12 ± 6 days for the patients in both treatment arms. The tendency for bleeding, the need for blood transfusion, the incidence of in-hospital reinfarctions, the need for emergency procedures (coronary angioplasty, bypass operation, electroconversion, pacemaker insertion or cardiopulmonary resuscitation), congestive heart failure at discharge and mortality were all higher among the patients in the invasive treatment group. The total rate of complications was 36 and 27% in the invasive and conservative groups, respectively, but this difference was not significant. A similar trend in favor of the patients in the conservative treatment group was also observed when patients with and without increased risk were analyzed separately (Table III).

Left ventricular function: Immediate radionuclide ventriculography data were available for 85 and 90% of the patients in the invasive and the conservative groups, respectively. PredischARGE radionuclide ventriculography data were available for 94 and 92% of the patients in the conservative and invasive groups, respectively. There was no difference between treatment groups in the mean immediate or predischARGE radionuclide left ventricular ejection fraction whether the patients did or did not have an increased risk (Table IV). Resting left ventricular ejection fraction and its change after exercise were also similar 8 weeks after admission in the 2 groups (Table IV).

Follow-up: Mean follow-up periods did not differ significantly for the patients in the invasive and conservative treatment groups (19 ± 4 and 21 ± 4 months, respectively). During clinic visits, the prevalence of anginal syndrome (13 vs 14%) and congestive heart failure (2 vs 3%) were similar in both groups. The incidence of positive effort-tolerance test results during radionuclide ventriculography was 19% for both treatment groups. The lack of difference between the invasive and conservative treatment groups persisted when the analysis was

TABLE V Mortality in the Invasive and Conservative Groups with Relation to Catheterization

	Treatment		p Value
	Invasive (n = 97)	Conservative (n = 104)	
Total mortality	8	4	0.15
Mortality during initial hospitalization			
<72 hours	2	4	NS
≥ 72 hours	3	0	NS
During follow-up			
Cardiac	2	0	NS
Noncardiac	1	0	NS
Total occurring 72 hours or later*	5	0	0.02

* Cardiac mortality ≥ 72 hours, the time of the scheduled angiography in the invasive group.
NS = not significant.

separately conducted for the patients with and without increased risk.

A significantly higher incidence of rehospitalization was observed among patients assigned to the conservative treatment group than in the invasive treatment group (29 vs 16%) ($p = 0.04$). Rehospitalizations were more frequent among patients with a history of angina before the initial hospitalization compared with those without such history in both the invasive (33.3 vs 10.1%) and conservative (38 vs 20%) ($p = 0.005$). Most of the patients who were rehospitalized in the conservative group had no history of angina, but this trend was not significant ($p = 0.12$).

A multivariate analysis was conducted to identify patients with increased risk for rehospitalization. This analysis took into account the following variables: study group, age, sex, infarct location, history of angina pectoris, diabetes mellitus, extent of coronary vessel disease, coronary angioplasty, immediate and discharge radionuclide left ventricular ejection fraction, and reinfarction during initial hospitalization. A history of angina pectoris was the only independent predictor of rehospitalization (relative risk 3.87, $p < 0.01$). Among the 128 patients who underwent coronary angiography, 67% of those with a history of angina had 2- to 3-vessel coronary artery disease compared with only 40% of the patients without a history of angina ($p = 0.03$).

During the follow-up period, 3 patients in the invasive group and 4 patients in the conservative treatment group had acute reinfarctions.

Mortality: Nine patients died before discharge, 5 among the 97 patients assigned to the invasive group (5%) and 4 among the patients assigned to the conservative group (4%) (Table V). Of these, 2 of the deaths in the invasive group and all 4 of the deaths in the conservative group occurred within the first 72 hours after enrollment; that is, before the scheduled angiography in the invasive group. In the invasive group, 3 deaths occurred 72 hours or later after admission and 2 of these deaths occurred shortly after coronary angiography or angioplasty; 1 patient had asystole followed by resistant ventricular fibrillation and death, and the other had a

ruptured myocardium the day after coronary angiography was performed. Both patients were stable hemodynamically before the invasive procedure.

Three more deaths occurred during the follow-up period, all among patients in the invasive group. Of these, 2 were of cardiac cause and 1 was caused by malignancy. Two cardiac deaths occurred in patients who underwent coronary artery bypass operations and 1 of them died only a few days after a seemingly successful operation was performed. The total mortality rate for the follow-up period in the invasive group was thus double that for the conservative group, but the difference did not reach significance (8 vs 4%, $p = 0.15$). However, 5 of the total 8 deaths in the invasive group and none of the 4 total deaths in the conservative group occurred after the time of the scheduled angiography in the invasive group. When only the rates of these deaths were compared, the excess mortality in the invasive group became significant (5 of 91 vs 0 of 100, $p = 0.02$).

DISCUSSION

Recently it has been shown that angioplasty immediately after successful thrombolysis does not augment clinical outcome and is associated with a higher rate of complications.^{4,5} These complications may be due to intraluminal thrombi, intimal disruption, subintimal hematoma or platelet aggregation—characteristics of the infarct artery that may resolve with time. Thus, the lack of benefit conferred by angioplasty in the ECGS and the TIMI IIB trials might have been due to the timing of the procedure, which in 1 trial immediately followed thrombolysis and in the other was performed early after thrombolysis. Because angioplasty can be delayed for a few days in most patients who receive thrombolytic therapy, the question remained whether routine late catheterization might still be superior to conservative management.

Our study addressed this question by delaying the cardiac catheterization of patients randomized to our invasive treatment group by ≥ 72 hours after enrollment (mean 5 days). We found that even when routine angiography and angioplasty were delayed, it conferred no benefit when compared with conservative treatment consisting of angiography and angioplasty only when indicated by recurrent postinfarction angina or exercise-induced ischemia.

Our results are consistent with those of 2 previous studies comparing invasive and conservative treatments after thrombolytic therapy with rt-PA. In the ECGS trial,⁶ 367 patients were randomly assigned to immediate (median, 42 minutes after treatment initiation) angiography and angioplasty, or to an identical conservative treatment that omitted routine angiography. In the TIMI IIB trial,⁷ 3,262 patients were randomized into invasive treatment that consisted of coronary angiography and angioplasty performed a mean of 32.5 hours after treatment initiation, and conservative treatment with angiography and angioplasty only for patients who had spontaneous or exercise-induced ischemia. In the TIMI trial, 25% of the patients in the conservative limb had interventions at 42 days, whereas only 6% of patients in the invasive limb actually underwent angio-

plasty or operation. In both studies, conservative management was associated with a lower rate of complications and a nonsignificant decrease in mortality.

Despite the threefold higher incidence of bypass surgery and twofold higher incidence of angioplasty, 10-month mortality was not improved in the invasive treatment group compared with the conservative treatment group. In addition, left ventricular function was not improved among the survivors in the invasive treatment group compared with survivors in the conservative group. Furthermore, patients in the conservative group had fewer reinfarctions, emergency procedures, bleeding complications and incidences of congestive heart failure at discharge than patients in the invasive group, although these differences were not significant.

Guerin et al¹⁰ and the TIMI IIB investigators⁷ documented an increase in left ventricular ejection fraction from rest to exercise in postinfarction patients assigned to angioplasty. In contrast, we found only a small and insignificant increase in left ventricular ejection fraction among patients who had angioplasty during the exercise radionuclide ventriculography performed at the 2-month follow-up visit.

We have no explanation for the similarities in coronary anatomy between the patients in the invasive group, all of whom underwent angiography regardless of their clinical status, and the patients in the conservative group who were selected for catheterization because of clinical signs of myocardium at risk. These results once again demonstrate the lack of correlation between the severity of clinical symptoms and angiographic patterns and strengthen our conclusion that the decision to proceed to mechanical revascularization should be based on both clinical and angiographic indicators, rather than just on the severity of the infarct-artery lesion.

There was a significantly higher rate of rehospitalizations in patients assigned to the conservative treatment arm. Preinfarction angina pectoris was significantly associated with an increase in rehospitalization in both invasive and conservative treatment groups, even after all related variables were accounted for. In fact, history of angina was the only independent predictor of rehospitalization. Multivessel coronary disease was more prevalent in patients with a history of angina than in those without such history, an observation consistent with an earlier study.¹¹ Thus, the increase in rehospitalizations among patients with angina may stem from a poorer baseline coronary anatomy. This theory is also consistent with an earlier observation that in patients with a first acute MI, preinfarction angina is significantly associated with a higher incidence of postinfarction angina, as well as a higher mortality 3 years after the initial hospitalization.¹²

Our data indicate that selective coronary intervention in patients for whom invasive treatment is indicated by clinical signs is associated with a clinical outcome at least as good as that obtained by routine coronary intervention for all patients, regardless of whether the intervention is performed early or late during hospitalization.

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Prognostic Use of a QRS Scoring System After Hospital Discharge for Initial Acute Myocardial Infarction in the Framingham Cohort

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Myocardial infarct size is an important risk factor for survival after acute myocardial infarction (AMI). The purpose of this study was to determine the prognostic value of myocardial infarct size, as estimated by the Selvester 54-criteria/32-point QRS scoring system, in the Framingham cohort. During the first 30 years of the Framingham Heart Study, a total of 384 participants developed an AMI requiring hospitalization; from this group, 243 patients met the following inclusion criteria: (1) no electrocardiographic changes due to a previous infarction, (2) survival >3 days after discharge from the AMI hospitalization and (3) no electrocardiographic evidence of conduction disturbances or ventricular hypertrophy at the time of their final in-hospital electrocardiogram. Univariate and multivariate analyses were performed to test the association of the QRS score, and other associated risk factors, with time until coronary heart disease-related death. QRS score was found to be significantly associated with outcome ($p = 0.03$), as was the systolic blood pressure before infarction ($p > 0.001$). Both univariate and multivariate analysis showed that a history of systolic hypertension was the variable most strongly associated with coronary heart disease-related death. Thus, identification of AMI survivors at high risk for subsequent mortality can be improved by routine blood pressure measurement before AMI, and QRS scoring of the electrocardiogram taken at hospital discharge.

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Reports from the Framingham Heart Study¹⁻³ and others⁴⁻⁶ indicate high early mortality rates after acute myocardial infarction (AMI). Kannel et al¹ reported 1-year mortality rates of 20% for men and 45% for women experiencing their first AMI. Such mortality rates are closely related to both the amounts of infarcted^{7,8} and of persistently jeopardized myocardium.⁹ Several techniques exist for estimating the amount of infarcted myocardium; one method that is readily available and adaptable to population- and community-based studies is the Selvester 54-criteria/32-point QRS scoring system,¹⁰ which uses the standard 12-lead electrocardiogram.

Previous reports using the Selvester scoring system have determined its specificity in normal subjects,^{10,11} validated its accuracy with anatomical techniques for estimating AMI size¹²⁻¹⁴ and compared it to predicted ejection fraction after AMI.¹⁵⁻¹⁸ Biochemical^{16,17,19} and angiographic^{16,18} correlations have been made, and the QRS score has been tested as an index for survival after AMI.^{9,16} The present study evaluates the prognostic significance of the Selvester scoring system in a cohort of patients after their first AMI in the context of other clinical data available from the Framingham Heart Study.^{1,2}

METHODS

Inclusion criteria: Three hundred eighty-four Heart Study participants had been judged on the basis of chest pain and electrocardiographic changes to have an initial clinically documented AMI during the first 36 years of follow-up. Twenty-four patients with the following electrocardiographic abnormalities were not included in this study because similar patients have routinely been excluded from previous QRS scoring validation studies¹⁰⁻¹⁴: left or right ventricular hypertrophy, left or right bundle branch block, left axis deviation ($\geq -45^\circ$), right axis deviation ($\geq +120^\circ$) or ventricular pacing (Table I). After careful review, we included the 243 patients who met historical and electrocardiographic criteria for initial AMI diagnosis, had evaluable medical records and survived through the third hospital day after the AMI. Previous studies have shown that patients can be expected to achieve their stable level of QRS changes by the third day after AMI.²⁰

Myocardial infarction diagnosis: The medical records of Heart Study participants were reviewed after each biennial examination for indications of cardiovas-

cular disease. An AMI was diagnosed when there was prolonged chest pain that resulted in hospitalization (or, in the earliest years, immediate medical attention) with serial electrocardiographic changes including: transient ST-segment elevation with subsequent T-wave inversion and persistent loss of initial positive QRS forces. The decision regarding AMI diagnosis was reached by a panel of Framingham investigators according to established Heart Study definitions and protocol.²¹⁻²³

QRS scoring: The complete 54-criteria/32-point Selvester QRS scoring system¹⁰ was applied to the final in-hospital standard 12-lead electrocardiogram that had been obtained for each patient. Each point in the scoring system represents an infarction of approximately 3% of the left ventricle.²⁴⁻²⁶ After QRS scoring of each electrocardiogram, patients were classified according to the estimated size of their AMI: small, <10% (0 to 3 points); moderate, 10 to 21% (4 to 7 points); and large, >21% (≥ 8 points). The 3 breakpoints were selected before any survival analysis was performed and subsequently are referred to as the "classified QRS scores." This variable was then coded 1, 2 or 3 and a coefficient was estimated in the regression analysis. The rationale for this breakdown was to attenuate the growth in relative risk, which might be quite substantial using the QRS score as a continuous variable in the subsequent analyses.

Covariables: From computerized files the following information was retrieved for the biennial examination preceding, and that following, each patient's initial AMI: (1) history of peripheral vascular disease (claudication, transient ischemic attack or stroke), (2) total serum cholesterol level (mg/dl), (3) obesity (Metropolitan relative weight), (4) systolic blood pressure, (5) systemic hypertension (sitting pressure exceeding 160/95 mm Hg), (6) smoking habit (cigarettes/day), (7) electrocardiographic evidence of left ventricular hypertrophy and (8) history of diabetes mellitus. Information preceding the AMI taken from up to 3 biennial examinations before the AMI.

Records from the AMI hospitalization were examined for the presence of the following variables: (1) AMI location, (2) worst Killip classification of heart

TABLE I Evaluable Patients

Recognized MI	384
Conduction abnormalities	25
AMI prior to admission	2
No AMI (by ECG review)	4
Silent AMI (by ECG review)	4
Died during hospitalization	68
Insufficient records	38
Total exclusions	141
Evaluable	243

AMI = acute myocardial infarction; ECG = electrocardiographic.

failure²⁷ during the AMI hospitalization, (3) electrocardiographic evidence of second- or third-degree atrioventricular block, (4) electrocardiographic evidence of ventricular tachycardia, (5) AMI extension diagnosed by recurrence of pain with subsequent new Q-waves or appropriate enzyme changes and (6) cardiac arrest.

Variables 3, 4 and 5 were considered "present" when documented in the record, "absent" when not mentioned in a complete record and "unknown" in an incomplete record. Cardiac arrest was considered absent if not specifically mentioned, regardless of the quality of the record. In 56 patients (25%) no Killip classification could be determined from the medical record; because of this difficulty, Killip classification was not added to any of the multivariate analyses as a tested variable.

The date and cause of death were recorded for each patient. Follow-up from the AMI hospitalization was divided into 2 periods based on the shape of the cardiac-related time-mortality curves (Figure 1). The point of final curve flattening was used to divide follow-up into "early" and "late" periods. From time of infarction, this point of flattening in the mortality curves appeared just after 60 days after discharge. Therefore, the interval between days 4 and 60 was considered the "early" time of high and changing mortality and that after day 60 the "late" time of low and stable mortality. This differentiation was consistent with a prior study that identified different predictors for early versus late mortality.⁹

Statistics: Logistic regression was used to test for associations between risk factors and death from any cause within the early follow-up period. For the remain-

FIGURE 1. Coronary heart disease-related death rate (CHD death rate)/day after initially diagnosed acute myocardial infarction (AMI) electrocardiogram (ECG) in 243 patients studied.

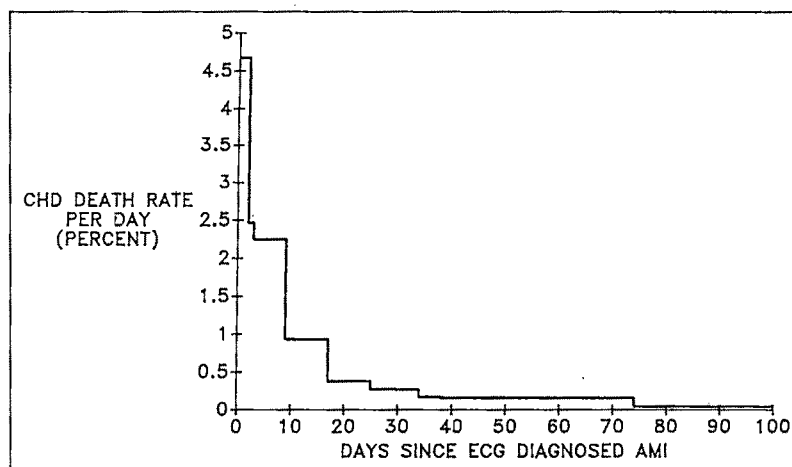


TABLE II Mean PredischARGE QRS Scores

Factor	Men		Women	
	Number	Mean QRS Score	Number	Mean QRS Score
All patients	174	6.6	69	6.4
Age (yrs)				
<55	65	7.6	6	7.7
55-64	65	5.4	23	6.0
≥65	44	6.7	40	6.4
AMI location				
Anterior	69	7.4	33	6.8
Inferior	96	6.1	32	5.8
Post/lateral	9	7.4	4	6.8
AMI extension				
No	97	6.5	40	6.2
Yes	13	9.3	4	7.0

AMI = acute myocardial infarction.

ing analyses, time from the AMI until coronary heart disease-related death was the outcome of interest. Survival of individuals not dying of heart disease was censored at their death date or at the eighteenth Heart Study examination.

Cox's proportional hazards model, as implemented by Harrell,²⁸ was used for testing the associations of the covariates with time until death. Associations of sex and age with time until death were performed to determine if the correlations were consistent in men and women and at all ages. Univariate tests of association were performed for each covariate of interest. The backward stepwise procedure provided by Harrell was used for multivariate analysis of the risk factors. The *p* value used for inclusion of variables in the multivariate model was 0.1. Least-squares regression analysis was used to test for differences in predischARGE QRS scores with the covariables.

RESULTS

The median age of the participants was 57 years for the 174 men (range: 37 to 85 years with 77% ≥65 years at AMI), and 65 years for the 69 women (range: 43 to 86 years with 46% ≥65 years at AMI). There was a 50% coronary heart disease-related death rate and a 23% other death rate during the prolonged follow-up period. Non-fatal complications were relatively infrequent, reflecting the community basis of the Framingham Heart Study.

Table II lists the results of the QRS scoring of the final predischARGE electrocardiograms. PredischARGE scores ranged from 0 to 16, with a 25th percentile of 4, median of 6 and 75th percentile of 9. QRS scores were highest in the younger patients, intermediate in the older patients and lowest in those patients in the middle age range.

The test for any difference in QRS score by age group was significant for men (*p* > 0.01), but not for women. Individual age-group comparisons in men showed the 55- to 64-year-old group to have significantly lower scores than either of the other 2 age groups. Testing for differences in QRS score after adjusting for age showed that men with inferior AMIs had signifi-

TABLE III Time Until CHD Death Univariate Cox Regression Coefficients

Variable	Men*	Women*	All†
Measurements taken during MI hospitalization			
QRS score	0.07‡	0.01	0.06‡
QRS score (classified)	0.46§	0.17	0.41§
QRS >3	1.50§	-0.25	1.00§
CHF Killip class	0.32	1.10	0.49§
MI extension	0.11	-6.30	-0.01
Second-degree block	-0.60	-7.70	-0.75
Third-degree block	0.65	-5.4	0.36
Inferior MI	-0.24	-0.42	-0.27
Ventricular tachycardia	-0.46	0.11	-0.33
Measurements taken before or during MI hospitalization			
Metric relative weight	0.01	0.01	0.01
Serum cholesterol	0.0035	-0.012	0.0004
Systolic BP	0.017§	0.023‡	0.018§
Systemic hypertension	0.36	0.20	0.34
Cigarettes/day	0.010	0.022	0.013
Smoker	0.13	0.67	0.24
LVH by ECG	0.32	1.00	0.57
Diabetes mellitus	0.13	1.20‡	0.51

* Analyses stratified by age group (<55, 55-64, ≥65).

† Analyses stratified by age group (<55, 55-64, ≥65) and sex.

‡ *p* < 0.05; § *p* < 0.01.

BP = blood pressure; CHD = congestive heart disease; CHF = congestive heart failure; ECG = electrocardiogram; LVH = left ventricular hypertrophy; MI = myocardial infarction.

cantly lower scores than those with anterior infarctions (*p* = 0.02). The trend was the same in women, but the difference was not significant. As one might expect, after adjusting for age and sex differences, those with AMI extension demonstrated significantly higher QRS scores than those without such extensions.

No significant association could be ascertained between QRS score and mortality during the early follow-up period. The only variable that achieved prognostic significance for this period was Killip classification. Table III summarizes the univariate Cox regression coefficients for the late period. Both the raw and the classified QRS scores showed a significant association with time until coronary heart disease-related death in the univariate analysis (*p* > 0.05). These relations, however, attained significance only in men.

The multivariate model for men included only coefficients for QRS score and systolic blood pressure before the AMI and QRS score. Table IV lists the Kaplan-Meier estimates of 10-year coronary heart disease mortality for men according to age, QRS score and systolic blood pressure. When the QRS score is <3, there is no mortality in the youngest patients and low mortality in both older groups. Too few women were available to perform an analysis similar to the multivariate model applied to the men.

DISCUSSION

The consensus of previous studies is that a patient's AMI size and severity of the coronary artery disease are 2 of the most important predictors of survival after AMI.^{6-8,29-32} The latter most likely is related to its threat to remaining viable myocardium, as would be indicated by angina after AMI,³³ resting ST depression³² or a positive stress test.^{34,35} Infarct size may affect mortality in 2 distinct ways: large infarcts may result in left

ventricular failure or an "arrhythmogenic myocardium." Either condition may cause death, even in the absence of any subsequent ischemic event.

Califf et al^{36,37} have documented associations between the amount of infarcted myocardium (as indicated by either QRS changes or wall motion abnormalities), a high level of ventricular premature beats on Holter monitoring and sudden death. Bolick et al³⁸ have attempted to identify the specific anatomical characteristics of those patients who die after an AMI either with or without prior documented ventricular tachycardia. Those with ventricular tachycardia have larger infarcts, greater aneurysmal dilatation and more ventricular hypertrophy.

Lown and Wolf³⁹ have found that exercise tests are poor predictors of the development of ventricular tachycardia or fibrillation in patients with poor ventricular function and frequent premature beats. Several experimental studies⁴⁰⁻⁴² have demonstrated that large, but not small, remote infarcts lower the threshold to ventricular fibrillation in the absence of further myocardial ischemia.

In the present study, death within 60 days of the AMI was not associated with the QRS score. This result is consistent with that reported by Waters et al,⁹ which identified different predictors for early versus late mortality. In that study, however, follow-up periods were divided into first and second years rather than into intervals of steep and flattened portions of time-mortality curves. A relatively long time would be expected to elapse between an initial AMI and death from heart failure. The time after AMI when the "arrhythmogenic" myocardium most likely might precipitate ventricular fibrillation has not been established. However, etiologic factors that require time to develop, such as aneurysm formation⁴³ and periinfarction hypertrophy,³⁸ have been implicated.

The other principal cause of mortality after AMI, residual ischemia, has been shown to be most important during the initial period. The Waters study identified residual ischemia as most prognostic during the first year, and QRS-estimated infarct size as most prognostic during the second year after AMI.⁹ Indeed, QRS score had little prognostic ability during the earlier period after AMI. It is likely that future studies will document a transition period during the first year after when the most significant pathophysiologic risk factor changes from residual ischemia to AMI size.

Univariate analysis showed that the classified QRS score imparted an increased relative risk as the size of the infarction increased from small to moderate to large. The QRS score was originally classified in this way because it was anticipated that the Cox model would not show a statistically significant association between raw QRS score and time until coronary heart disease-related death. Using the actual QRS score, however, the Cox model did show a statistically significant result ($p = 0.05$).

This study has reaffirmed the long-standing association of preexisting hypertension with mortality after AMI; Kannel et al¹ reported that blood pressure levels in a group of 193 hypertensive men, preceding an initial

TABLE IV Kaplan-Meier Estimates of CHD Death by Age Group

	Age at AMI		
	<55	55-64	65+
Classified QRS Score			
≤3	0 (1/9)	18 (6/18)	13 (1/7)
4-7	44 (16/23)	17 (14/25)	85 (10/18)
≥8	37 (15/33)	44 (13/19)	67 (8/14)
Systolic blood pressure before AMI			
<140	27 (15/37)	25 (17/33)	48 (4/9)
≥140	47 (17/28)	28 (16/29)	68 (15/30)

Numbers in parentheses represent the total number of CHD deaths observed for all follow-up and total number followed for each group with non-missing values. Other numbers are percentages.
AMI = acute myocardial infarction; CHD = congestive heart disease.

AMI, were related to survival. In that study, previously hypertensive patients were found to have almost 3 times the mortality of normotensive patients; however, blood pressure levels after recovery from the initial AMI were unrelated to subsequent 5-year survival.

Although any predictive technique has limitations, the Selvester QRS scoring system at the time of hospital discharge from an initial AMI can supply useful information. In particular, measurement of the QRS score in the immediate postinfarction period is predictive of long-term outcome. Prognostic factors based on the amount of residually ischemic myocardium, rather than those related to the amount of already infarcted myocardium, would be expected to have their maximal value during the earlier period.

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Comparison of Early Exercise Treadmill Test and Oral Dipyridamole Thallium-201 Tomography for the Identification of Jeopardized Myocardium in Patients Receiving Thrombolytic Therapy for Acute Q-Wave Myocardial Infarction

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Thrombolytic therapy has become the treatment of choice for patients with acute myocardial infarction. Researchers are not yet able to identify patients with salvage of myocardium who are at risk for recurrent coronary events. Thus, a prospective trial was performed in 46 patients with myocardial infarction (28 anterior and 18 inferior) who received thrombolytic therapy to determine if early thallium tomography (4.7 days) using oral dipyridamole would identify more patients with residual ischemia than early symptom-limited exercise treadmill tests (5.5 days).

There were no complications during the exercise treadmill tests or oral dipyridamole thallium tomography. Mean duration of exercise was 11 ± 3 minutes and the peak heart rate was 126 beats/min. Thirteen patients had positive test results. After oral dipyridamole all patients had abnormal thallium uptake on the early images. Positive scans with partial "filling in" of the initial perfusion defects were evident in 34 patients. Angina developed in 13 patients and was easily reversed with intravenous aminophylline.

Both symptom-limited exercise treadmill tests and thallium tomography using oral dipyridamole were safely performed early after myocardial infarction in patients receiving thrombolytic therapy. Thallium tomography identified more patients with residual ischemia than exercise treadmill tests (74 vs 28%). Further studies are required to determine whether the results of thallium tomography after oral dipyridamole can be used to optimize patient management and eliminate the need for coronary angiography in some patients.

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Thrombolytic therapy has now become the treatment of choice for most patients presenting in the early hours of acute myocardial infarction. Because of the incomplete nature of their myocardial infarction, many patients are at risk for recurrent cardiac events; thus, it is important to identify these patients early.¹⁻³ In patients receiving thrombolytic therapy, clinical and laboratory variables are helpful but they cannot be used reliably to identify patients with reperfused coronary arteries.⁴ Although coronary angiography can be performed in all patients to determine the patency of the infarct vessel, and balloon angioplasty can be used in patients with suitable anatomy, this approach has not been found to be superior to the conservative strategy of intervention only in patients with recurrent ischemia.⁵⁻¹⁰ Because of baseline electrocardiographic abnormalities, antiischemic therapy and diminished exercise tolerance after myocardial infarction due to prolonged bed rest, we hypothesized that thallium imaging using oral dipyridamole, which is independent of these factors, may be superior to exercise treadmill tests.¹¹⁻¹⁵ We performed a prospective study to determine whether dipyridamole thallium imaging early after myocardial infarction would identify more patients with ischemia than symptom-limited exercise treadmill tests. Oral dipyridamole was used since intravenous dipyridamole is not yet approved by the Food and Drug Administration.

METHODS

All patients who were given thrombolytic therapy and were treated by one of us (AJ) between December 1987 and March 1989 were entered into this study. We identified 58 patients, but 12 patients were subsequently excluded for the following reasons: 2 died before the study, 4 had spontaneous ischemia with electrocardiographic changes necessitating intervention, 1 had bilateral lower limb amputation, 1 refused the study, 3 had non-Q-wave infarctions and 1 had previous bypass surgery. Coronary angiography was performed before both tests between 1 and 4 days. No patient was excluded from the study as a result of the angiographic findings.

Coronary angiography, thallium tomography using oral dipyridamole, and symptom-limited exercise treadmill tests were performed in 46 patients (35 men and 11

TABLE I Results of the ETT and DP-Tl (n = 46)

	ETT	DP-Tl
Days after infarction	5.5 (range 3-10)	4.7 (range 3-11)
HR "rest" (mean beats/min)	80	78
HR "peak" (mean beats/min)	126	85
BP "rest" (mean mm Hg)	111	121
BP "peak" (mean mm Hg)	149	114
Duration (minutes)	11 (range 3-15)	—
Chest pain	17	13
Myocardial ischemia	13	34
Infarct zone only	—	22
Infarct and non-infarct zone	—	7
Non-infarct zone only	—	5

BP = blood pressure; DP-Tl = oral dipyridamole thallium tomography; ETT = exercise treadmill test; HR = heart rate.

women). Mean age was 55 years (range 35 to 71). Four patients had a history of myocardial infarction. Mean time from the onset of chest pain to administration of intravenous thrombolytic therapy (44 tissue plasminogen activator and 2 streptokinase) was 2.8 hours. Twenty-eight patients (61%) had anterior wall acute myocardial infarction and 18 patients (39%) had an inferior wall myocardial infarction. Mean peak creatine kinase was 1,791 IU/liter (range 200 to 6,500).

Coronary angiography: Coronary angiography and ventriculography were performed using the Judkins technique. Significant stenosis was defined as >50% narrowing in 1 or more of the epicardial coronary arteries. Left ventricular angiograms were performed in the 30° right anterior oblique projection.

Exercise treadmill tests: Symptom-limited exercise treadmill tests were performed using an automated programmable treadmill. The modified Bruce protocol was used in 43 patients and the standard Bruce protocol in 3 patients. The exercise test was considered positive if there was a flat or downsloping ST-segment depression of ≥ 1 mm. It was considered negative if there was <1 mm of ST-segment depression at a heart rate of >85% predicted for age. The exercise test was considered nondiagnostic if there was no significant ST-segment depression at a heart rate of <85% predicted for age. Development of chest pain was noted, but was not considered positive for ischemia.

Dipyridamole thallium tomography: On the day of study, all patients received their oral medications with sips of water. After placement of an intravenous line, patients received 300 mg of oral dipyridamole tablets, which were crushed and mixed in 50 ml of water. Leads II, V₁ and V₅ were continuously recorded while the patients were in the nuclear cardiology laboratory. A 12-lead electrocardiogram, blood pressure and heart rate were recorded at baseline and then every 15 minutes for 45 minutes. Thallium was injected at 45 minutes, or earlier, if there was significant angina or evidence of myocardial ischemia on the electrocardiogram. Intravenous aminophylline (50 to 150 mg) was administered over 1 to 2 minutes at least 5 minutes after thallium injection to patients who developed chest pain or evidence of ischemia as manifested by ST-segment depression. Early tomographic images and the delayed (4-hour) redistribution images were obtained in all patients. Repeat images were obtained at 24 hours in patients with no evidence of redistribution on the 4-hour images.

Tomographic images were obtained using a rotating gamma camera (GE-STARCAM). An arc of 180° was used, spanning from 45° left posterior oblique to the 45° right anterior oblique positions. The myocardial segments were visually interpreted in the short, horizontal long and vertical long axes for the presence of perfusion abnormalities and redistribution by 3 physicians who were unaware of the results of coronary angiography. The septum and the anterior segments corresponded to the left anterior descending coronary artery, the inferior and posterior segments corresponded to right coronary artery, and the lateral segments corresponded to the circumflex coronary artery. The apex did not define any particular vascular distribution.

Statistical methods: Data are reported as mean \pm standard deviation. Comparison of discrete variables was made using paired *t* test. A *p* value <0.05 was considered significant.

RESULTS

Coronary angiography: Left ventricular angiograms in the right anterior oblique projection showed ventricular asynergy in all patients. Mean global ejection fraction was 49% (range 26 to 77%). One patient had a 50%

TABLE II Comparison of the Positive and Negative Exercise Treadmill Tests (ETT) and Ischemic and Nonischemic Single-Photon Emission Computed Tomography (SPECT)

	ETT +	ETT -	p Value	SPECT +	SPECT -	p Value
Pts	13	33		34	12	
Age (yrs)	60	53	<.05	56	53	NS
Meds	1.6	1.8	NS	1.7	1.8	NS
Peak CK	1,143 \pm 428	2,072 \pm 1,520	<0.01	1,428 \pm 996	2,846 \pm 1,727	<0.05
EF (%)	50 \pm 8	49 \pm 13	NS	47 \pm 12	53 \pm 10	NS
Diseased vessels	2.0	1.7	NS	1.9	1.7	NS
S/P MI days	5.7 \pm 2.5	5.4 \pm 1.5	NS	4.7 \pm 2.1	4.5 \pm 0.7	NS
Duration (min)	9.8	11.1	NS	—	—	
Chest pain	7	13		13	0	
"Stress" HR (beats/min)	114	131	<0.01			

CK = creatine kinase; EF = ejection fraction; HR = heart rate; Meds = medications; MI = myocardial infarction; NS = not significant; S/P = status post; + = positive, - = negative.

diameter stenosis on the left main coronary artery; 12 patients had 3-vessel disease, 14 patients had 2-vessel disease, 18 patients had 1-vessel disease, and 2 patients had a single narrowing of <50% diameter. The infarct-related vessel was the left anterior descending in 28 patients, the right coronary artery in 16 patients and the circumflex coronary artery in 2 patients. The infarct-related vessel was open with Thrombolysis in Myocardial Infarction grade 2 or better flow in 32 patients (70%) (left anterior descending in 20 of 28, right coronary artery in 11 of 16 and the circumflex coronary artery in 1 of 2 patients). Mean residual stenosis of open infarct-related vessels was 86%. All patients with totally occluded infarct vessels had collaterals filling the distal segments. Only 4 patients with an open infarct-related vessel had a residual stenosis of <70%.

Treadmill exercise stress tests: Symptom-limited exercise treadmill tests were performed at a mean of 5.5 days (range 3 to 10 days) after myocardial infarction. All patients were receiving cardiac medications (20 β -adrenergic blockers, 25 calcium antagonists and 36 nitrates) and none were receiving digoxin. No patient had a left bundle branch block. During the study no patients developed ventricular tachycardia, hypotension or a prolonged episode of angina requiring intervention. Exercise was terminated for the following reasons: severe dyspnea or claudication (41), severe angina (3) and ST-segment depression of >2 mm (2). Mean duration of exercise was 11 minutes (3 to 15 minutes). The heart rate and the blood pressure significantly increased from 80 ± 15 to 126 ± 20 beats/min and 111 ± 12 to $149 \pm$

20 mm Hg, respectively. Exercise tests were positive in 13 patients (Table I). Three of these patients had increasing ST elevation with exercise and new ST depression. Chest pain developed in 7 of 13 patients with positive tests, 4 of 14 patients with negative tests and 6 of 19 patients with nondiagnostic tests. Among patients with nondiagnostic tests, 16 had an inadequate heart rate at peak exercise even though they exercised for a mean duration of 11 minutes, which was not significantly different than the remaining patients. It was often difficult to be certain if the chest pain in these 10 additional patients was similar to the infarction pain. Therefore, only 13 (28%) patients were considered to have a positive test. Patients with positive tests had a lower peak creatine kinase (1,143 vs 2,072 IU/liter [$p < 0.01$]), but the ejection fraction was similar (50 vs 49% [difference not significant]). Mean number of coronary arteries with stenosis >50% was similar in patients with positive and negative tests 2.0 versus 1.7 (difference not significant), respectively. Patients with positive tests exercised for shorter duration (10 vs 11 minutes [difference not significant]) and to lower heart rates (114 vs 131 beats/min [$p < 0.01$]) than patients with negative tests (Table II).

Oral dipyridamole thallium tomography: Oral dipyridamole thallium tomography was performed at a mean of 4.7 days (range 3 to 11) after myocardial infarction. All patients were receiving anti-anginal medications. After ingestion of 300 mg of oral dipyridamole, there was a significant increase in heart rate from 78 ± 13 to 85 ± 14 beats/min ($p < 0.05$) and a significant decrease in the blood pressure from 121 ± 15 to 114 ± 16 mm Hg ($p < 0.05$) (Table I). None of the patients developed ventricular arrhythmias or significant hypotension nor did any patients have any evidence for reinfarction by electrocardiogram or reevaluation of creatine

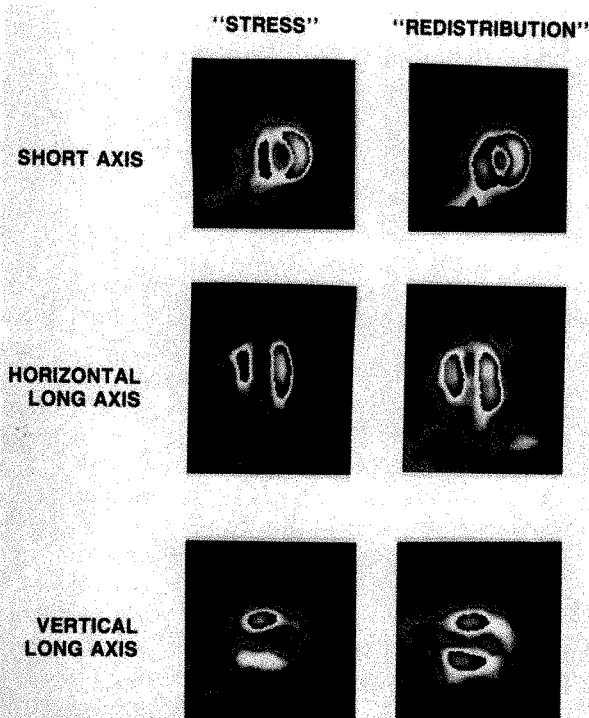


FIGURE 1. Thallium images showing areas of hypoperfusion on the anterior septal and inferior segments on the images on the left with partial redistribution in all segments on the images on the right.

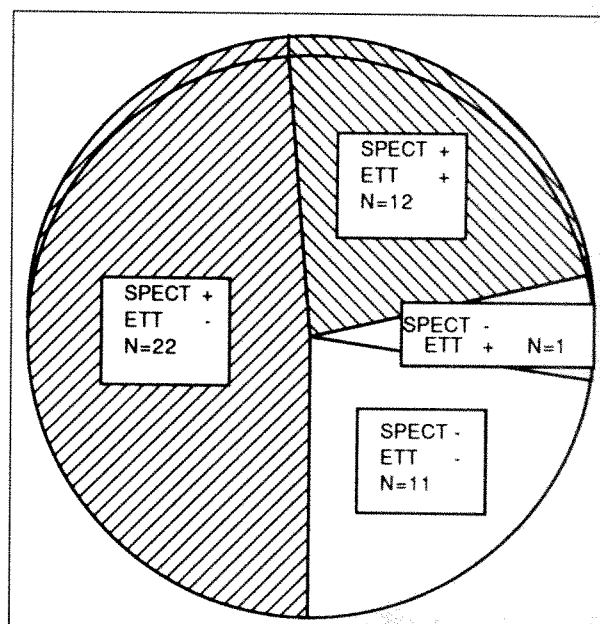


FIGURE 2. Pie diagram showing patients with positive and negative exercise treadmill test (ETT) and thallium-201 single-photon emission computed tomography (SPECT).

kinase. During the study, 13 patients (28%) developed angina and had ST-segment changes. Thallium was injected before 45 minutes in 4 of these patients. One additional patient had electrocardiographic evidence of ischemia without symptoms. The symptoms of angina and ST-segment changes in these 14 patients resolved promptly with the administration of aminophylline (75 to 150 mg). Due to severe headache, 6 additional patients received aminophylline.

Abnormal thallium tomographic images with diminished thallium uptake were present in all patients. Partial redistribution of thallium on the delayed (4 hours) images was evident in 32 patients. Of patients with no redistribution at 4 hours, only 2 had partial "filling-in" at 24 hours. Thus, 34 patients (74%) had residual ischemia after myocardial infarction (Table I). Of these 34 patients, 22 had redistribution only in the vascular territory of the infarct vessel. In 7 patients, redistribution was evident in a region supplied by the infarct vessel, as well as a non-infarct vessel (Figure 1). Thus, 29 patients (62%) had redistribution in the infarct zone suggesting residual myocardial ischemia. Ten patients with ischemia in the infarct zone had totally occluded infarct vessels but had intracoronary collaterals. Five patients with a fixed defect in the infarct zone had a reversible defect consistent with ischemia in the distribution of a non-infarct vessel. All patients with evidence of distal ischemia had multivessel disease. Fixed defects with no redistribution were present in 12 patients. As was noted in patients with positive exercise treadmill tests, patients with ischemia on the thallium studies also had a trend toward a smaller infarction as evidenced by peak creatine kinase (Table II).

Multivessel disease was present in 26 patients, 18 patients had 1-vessel disease and 2 patients had a single stenosis of <50%. All patients with multivessel disease had a perfusion abnormality on the early thallium scans. Redistribution suggestive of ischemia was evident in 21 of 26 patients with multivessel disease and in 13 of 18 patients with 1-vessel disease. Thallium scans showed multiple areas of hypoperfusion indicative of multivessel disease in only 13 patients. Of the 4 patients with residual stenosis of <70% of the infarct vessel, 2 had ischemia in the infarct zone and 2 had a fixed defect. The exercise treadmill test was positive in 10 patients with multivessel disease and 3 patients with 1-vessel disease. Of the 13 patients with positive stress tests, 12 had evidence of ischemia on thallium tomography (Figure 2).

DISCUSSION

Patients with non-Q-wave myocardial infarctions are known to have recurrent cardiac events.¹⁶⁻¹⁹ Patients receiving thrombolytic therapy who have reperfused infarct vessels with severe narrowing are also recognized to be at much higher risk for recurrent cardiac events.¹ Guerci et al²⁰ demonstrated a lower incidence of exercise-induced ischemia in patients who had balloon angioplasty after thrombolytic therapy. In addition, some investigators have suggested that patients with nonreperfused infarct vessels do benefit from balloon angio-

plasty.²¹⁻²³ Cigarroa et al²⁴ reported a lower morbidity in patients with open vessels to the infarct zone. These observations had led to the routine use of coronary angiography in patients after thrombolytic therapy and balloon angioplasty in patients with suitable anatomy.

This aggressive strategy is not supported by recent clinical trials, including the second phase of Thrombolysis in Myocardial Infarction (TIMI-II) trial.^{6,8} In the TIMI-II trial, aggressive strategy of routine intervention did not result in lower morbidity or mortality. Therefore, intervention only in patients with recurrent ischemia was advocated. The identification of high-risk patients who have residual ischemia becomes important for decisions regarding interventions.

The safety of heart rate-limited exercise treadmill tests performed 10 to 14 days after myocardial infarction is well recognized.^{16,25,26} To our knowledge, ours is the first report of early (5.5 days) symptom-limited exercise treadmill tests in patients receiving thrombolytic therapy. Exercise treadmill tests were performed within 5 days in 30 patients. Using the symptom-limited protocol, patients exercised to a high heart rate without any complications but only 13 patients (28%) had an ischemic response on the electrocardiogram. Multivessel disease was present in 10 of 13 patients. Thus, exercise stress tests were not helpful in patients with 1-vessel disease. Ten additional patients who had chest pain without electrocardiographic changes may have had ischemia. Thus, 23 patients (50%) had either electrocardiographic evidence of ischemia or chest pain alone.

Exercise treadmill tests are effected by the baseline electrocardiogram, the patient's ability to exercise and cardiac medications. A thallium study using dipyridamole is independent of these factors.¹²⁻¹⁴ We had no complications in these 46 patients using oral dipyridamole early (4.7 days) after myocardial infarction. Studies were performed within 5 days of myocardial infarction in 36 patients. Redistribution suggesting ischemia was more common (74%) than electrocardiographic evidence of ischemia during exercise treadmill tests (28%). Ischemia on thallium imaging was just as common in patients with 1-vessel disease as multivessel disease. Although multivessel disease was present in 26 patients, only 13 patients had abnormal perfusion in the distribution of more than 1 vessel suggesting presence of multivessel disease. It is conceivable that more patients with multiple perfusion abnormalities could have been identified using quantitative imaging.²⁷

The angiographic status of the infarct vessel did not correlate with the presence or the absence of redistribution in the infarct zone. Of the 14 patients with occluded infarct vessels, 10 patients had redistribution in the infarct zone indicating residual ischemia. The apparent "salvage" of tissue in these patients is probably related to the presence of collateral vessels.^{28,29} Patients with collateral vessels are known to have smaller myocardial infarctions. The early identification of these patients would permit early intervention and thus result in a higher probability of successful balloon dilatation.²¹⁻²³ Further studies are required to determine whether the results of thallium tomography using oral dipyridamole

early after myocardial infarction lack specificity or are appropriate for the identification of high-risk patients who would benefit from further invasive interventions after thrombolytic therapy.³⁰

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Coronary Collaterals Assessed with Myocardial Contrast Echocardiography in Healed Myocardial Infarction

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The epicardial coronary collateral vessels are visualized with coronary angiography, but this method does not provide significant information about the myocardial perfusion supplied with the collaterals. In this study, myocardial contrast echocardiography (MCE) was performed to assess the coronary collaterals in 29 patients with old myocardial infarction. MCE was performed by intracoronary injection of 2 ml agitated amidotrizoate sodium meglumine. The peak background-subtracted gray level (PGL) in the infarct area was determined from the digitized echocardiographic images obtained before and after injection into the noninfarct and donor artery. PGL was compared with the 3-point coronary angiographic grades of collaterals. PGL in the infarct area was significantly lower in patients with poor collaterals than in patients with moderate to good collaterals (5 ± 4 vs 18 ± 8 U mean \pm standard deviation, $p < 0.01$). PGL in the infarct area was <10 U in the 3 patients with severe asynergy despite the moderate to good collateral supply, suggesting that activity of the collaterals was not good enough to preserve the wall motion effectively.

It is concluded that (1) the degree of MCE enhancement in the infarct area generally corresponded to the collateral grades assessed with coronary angiography, and (2) MCE may provide a measure of the collateral perfusion.

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The development of collateral vessels in the obstructive coronary arteries plays an important role in the preservation of myocardial perfusion and hence left ventricular (LV) wall motion in patients with coronary artery disease.¹⁻¹¹ The grade of coronary collateral vessels has been assessed with coronary angiography or nuclear methods in patients. However, nuclear methods do have obvious inherent limitations with respect to their practicality. Coronary angiography only demonstrates the presence or absence of anatomic connection between the donor and recipient arteries, and therefore it provides little information about the activity of coronary collaterals. Myocardial contrast echocardiography (MCE) is a relatively new method that may provide information about regional myocardial perfusion. Thus, this method may be used to assess the collateral function at the level of coronary microcirculation or myocardium rather than at the level of epicardial coronary arteries. MCE has another advantage in assessing the coronary collaterals because it could provide information of transmural blood flow distribution.¹² This study examines whether coronary collateral perfusion is visualized with MCE, and compares findings of MCE with the collateral grading obtained with coronary angiography and the degree of LV wall motion abnormalities assessed with left ventriculography.

METHODS

Patients: The study population comprised 29 patients with anteroapical or inferior old myocardial infarction who fulfilled the following criteria: (1) adequate 2-dimensional echocardiographic images; (2) significant coronary collateral vessels observed on the coronary angiogram; (3) occlusion of left anterior descending or right coronary artery; and (4) right dominant coronary artery system. Nineteen were men and 10 were women (aged 38 to 78 years [mean 62]). Twelve of the 29 patients had collaterals from the left anterior descending to the right coronary artery and the other 17 had collaterals from the right to the left anterior descending coronary artery. Nine of the 29 patients had non-Q-wave infarction. Average interval between the time of infarction and the time of the cardiac catheterization was 20 ± 12 (mean \pm standard deviation) months. All patients gave informed consent for both cardiac catheterization and MCE protocol.

Wall motion abnormality was observed in the left ventriculogram in all patients. All patients were classified into 3 groups using the following criteria on the

basis of the degree of opacification of the epicardial segment of the recipient artery in the coronary angiogram¹³: (1) poor, filling of side branches only; (2) moderate, partial filling of the epicardial segment; (3) good, complete filling of the epicardial segment. LV wall motion was arbitrarily graded by a 3-point scale on the basis of angiographically determined regional ejection fraction: normokinetic (>40%), hypokinetic (10 to 39%) and akinetic or dyskinetic (<9%).

Myocardial contrast echocardiography: Two-dimensional echocardiographic images were obtained by a commercially available phased-array system (model SSH-65A ultrasound system, Toshiba Corporation, Japan) with a 3.75-MHz transducer. MCE was performed by imaging a parasternal short-axis view at the midpapillary muscle level during intracoronary injection of 2 ml amidotrizoate sodium meglumine (Urografin®-76), which was hand-agitated during its passage through a 3-way stopcock. Echocardiographic images were recorded by video tape recorder (model BR 6400, Victor Corporation, Japan) from approximately 10 seconds before the injection of the contrast agent until the contrast enhancement was no longer evident. Gain settings were adjusted at the beginning of each recording as low as possible and so that endo- and epicardium could be identified. They were not changed during the remainder of the study. Contrast agent was injected into the recipient (infarct) artery, and subsequently into the donor (noninfarct) artery of collateral vessels.

Echocardiographic analysis: The system used for the analysis of echocardiographic image was a commercially available microprocessor-based off-line echocardiographic viewing system consisting of a personal computer (model PC-9801, NEC Corporation, Japan) and

TABLE I Peak Background-Subtracted Gray Level (PGL) in Infarct Area During Recipient (Infarct) Artery Injection, and in Infarct and Noninfarct Area During Donor (Noninfarct) Artery Injection, and PGL Ratio of Infarct to Noninfarct Areas

	PGL in:			PGL Ratio
	Infarct Area by Recipient A. Injection	Infarct Area by Donor A. Injection	Noninfarct Area by Donor A. Injection	
Poor collateral group	7 ± 4	5 ± 4	25 ± 6	0.19 ± 0.14
Moderate collateral group	4 ± 4	16 ± 6	30 ± 9	0.56 ± 0.17
Good collateral group	6 ± 4	19 ± 10	32 ± 10	0.60 ± 0.25

A. = artery.

a high-speed image processor capable of digitizing echocardiographic fields in real time (models 68322 and 6400, NEXUS Corporation, Japan). This system was used to convert each 2-dimensional echocardiographic image in the video tape to a 512 × 512 pixel matrix image with 256 gray levels/pixel and to quantify the intensity of echocardiographic signals in the regions of interest that were outlined by the operator. End-diastolic echocardiographic images of the short axis midpapillary muscle plane of the left ventricle before and after MCE were used for analysis. Echocardiographic images of the left ventricle were divided into 3 segments based on the common coronary artery supply as described in

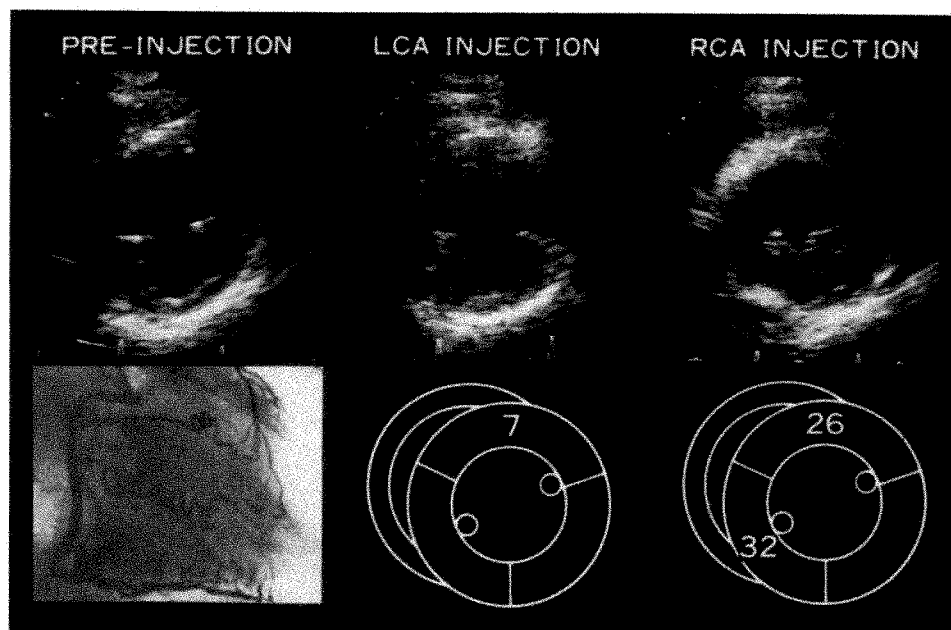


FIGURE 1. Myocardial contrast echocardiograms in a patient with anteroseptal infarction with good collateral vessels from the right coronary artery (RCA) to the left anterior descending artery. End-diastolic images before coronary artery injection (upper left panel) and after left coronary artery (LCA) injection (upper middle panel) and RCA injection (upper right panel). Lower left panel shows right coronary angiogram of this patient. Lower middle and right panels show the values of peak background-subtracted gray level in the corresponding region during LCA and RCA injections, respectively. Anteroseptal region shows good contrast enhancement during the RCA injection.

previous studies¹²: anteroseptal (left anterior descending artery supply), posterolateral (left circumflex artery supply) and inferior segments (right coronary artery supply). Each region of interest was traced by hand, excluding the strong echo signal of the endocardium and epicardium. In this study, the following 4 myocardial contrast echocardiographic parameters were determined in each patient: (1) the peak background-subtracted gray level (PGL) in the infarct area during the recipient (infarct) artery injection; (2) PGL in the infarct area during the donor (noninfarct) artery injection; (3) PGL in the noninfarct area during the donor (noninfarct) artery injection; (4) PGL ratio of the infarct to the noninfarct areas during the donor (noninfarct) artery injection. These parameters were independently determined by an observer who was blinded to coronary angiographic or left ventriculographic findings. The value for the quantitative analysis was determined as an average over 5 best-quality preinjection images and over 3 postinjection images where contrast enhancement was considered to be maximum.

Statistical analysis: All data are expressed as mean \pm standard deviation. Analysis of variance and Scheffé's test were used to compare the values among groups.

RESULTS

Visualization of coronary collaterals with myocardial contrast echocardiography: Injection of the contrast agent into the recipient (infarct) artery did not produce a significant contrast enhancement in the infarct area in any patients studied. There was no significant difference in PGL in the infarct area during the recipient artery

injection between any 2 of the 3 groups. Injection of the contrast agent into the donor (noninfarct) artery produced an apparent contrast enhancement in 1 of the 8 patients with poor collateral vessels, in 9 of the 10 patients with moderate collateral vessels, and in 9 of the 11 patients with good collateral vessels (Figure 1). PGL in the infarct area during the donor (noninfarct) artery injection and PGL ratio of the infarct to noninfarct areas were significantly higher in the moderate and good than in the poor collateral groups ($p < 0.05$, $p < 0.01$, and $p < 0.01$, $p < 0.01$, respectively) (Table 1). However, 3 patients in the moderate to good collateral group showed PGL of < 10 U in the infarct area during the donor (noninfarct) artery injection, and 4 patients showed a PGL ratio of < 0.4 (Figure 2, A and B). In these patients enhancement was observed only in the subepicardium (Figure 3).

Relation among myocardial contrast echocardiographic parameters, angiographic grading of collaterals and left ventricular wall motion: When the coronary angiographic grade and the degree of LV wall motion abnormalities were compared, there was a discrepancy in several patients (Figure 4). Left ventriculography revealed severe asynergy (regional ejection fraction of -11 to 7% [mean 1]) despite moderate or good collaterals in 6 patients. In these patients, contrast enhancement was not observed in the subendocardium but in the subepicardium of the infarct area during the donor (noninfarct) artery injection.

When the relation between parameters of MCE and the degree of LV wall motion abnormality was examined, PGL in the infarct area during the donor (noninfarct) artery injection was significantly lower in the

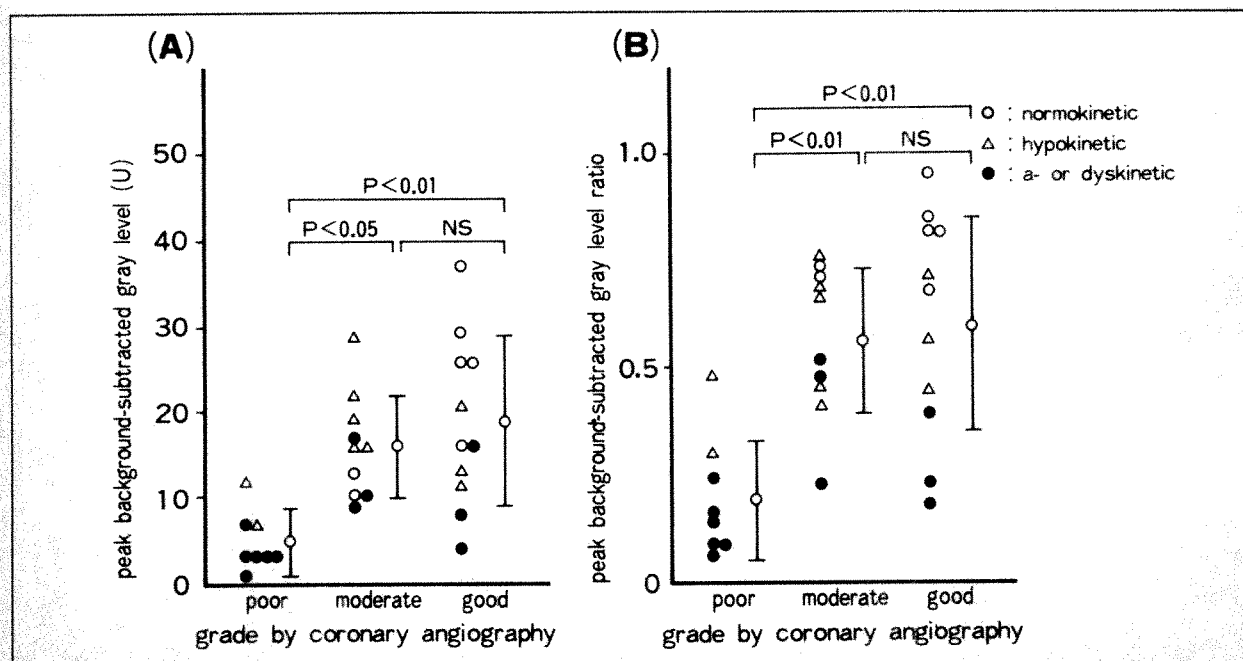


FIGURE 2. Relation among myocardial contrast echocardiographic parameters, the grade of collaterals assessed with coronary angiography and the degree of left ventricular wall motion abnormalities. Peak background-subtracted gray level (PGL) in the infarct area during the donor (noninfarct) artery injection (A) and PGL ratio of the infarct to noninfarct areas (B) was higher as the grade of collaterals obtained by coronary angiography was better. However, there were a few patients with low PGL and PGL ratio even in the group with moderate or good collaterals. a- = akinetic; NS = not significant.

akinetic or dyskinetic group than in the hypokinetic and normokinetic groups ($p < 0.05$, $p < 0.01$, respectively). PGL ratio of the infarct to noninfarct areas was also significantly lower in the akinetic or dyskinetic group than in the hypokinetic and normokinetic groups ($p < 0.01$, $p < 0.01$, respectively). These parameters of MCE were lower in the hypokinetic than in the normokinetic group ($p < 0.01$) (Figure 5, A and B).

DISCUSSION

We attempted to assess coronary collaterals from the degree of myocardial staining obtained with MCE. Parameters of MCE were compared with the 3-point coronary angiographic grade of coronary collaterals and the degree of LV wall motion abnormalities assessed with left ventriculography.

Assessment of myocardial perfusion: Quantification, rather than the presence or absence, of the contrast enhancement of the echocardiogram was investigated in the animal and clinical studies. Armstrong et al¹⁴ demonstrated that the peak contrast intensity accurately identified ischemic regions of LV myocardium in their study in which myocardial perfusion was simultaneously assessed with radioactive microspheres. Kemper et al¹⁵ showed that the degree of contrast enhancement can provide quantitative information about residual myocardial blood flow in ischemic regions by comparing myocardial contrast echocardiogram with radioactive microspheres findings. In contrast, Keller et al¹⁶ reported that peak contrast intensity did not correlate with absolute blood flows measured with radioactive microspheres because of the variability in the concentration and rate of injection of the microbubbles during each stage of ex-

periment. However, a recent clinical study¹⁷ showed that measurement of peak contrast intensity after intracoronary injections of contrast agent provides a relative index of myocardial perfusion that allows assessment of regional coronary reserve in patients with coronary artery disease. MCE was performed to assess the reaction for papaverine before and after coronary angioplasty in their study, and they obtained results indicating that after successful coronary angioplasty, peak intensity in the involved regions improved significantly during baseline contrast injections as well as during postpapaverine contrast injections.

Thus, the peak contrast intensity may be used to assess the regional myocardial blood flow. However, it is affected by several factors such as the injection rate, injection volume, and size of the microbubbles of the contrast agents. We attempted to reduce some of these effects by taking PGL ratio of the infarct to noninfarct areas.

Relation among myocardial contrast echocardiographic parameters, coronary angiographic grade of collaterals and left ventricular wall motion abnormalities: PGL in the infarct area during the donor (non-infarct) artery injection and PGL ratio of the infarct to noninfarct areas were greater as the coronary angiographic grade of the collaterals was better. However, PGL and PGL ratio were low despite good or moderate collaterals in a few patients. These patients with discrepant results between MCE and coronary angiography may be explained by the hypothesis that coronary angiography demonstrates only the anatomic connection between the donor and recipient arteries, but does not indicate the activity of coronary collaterals.^{18,19} In

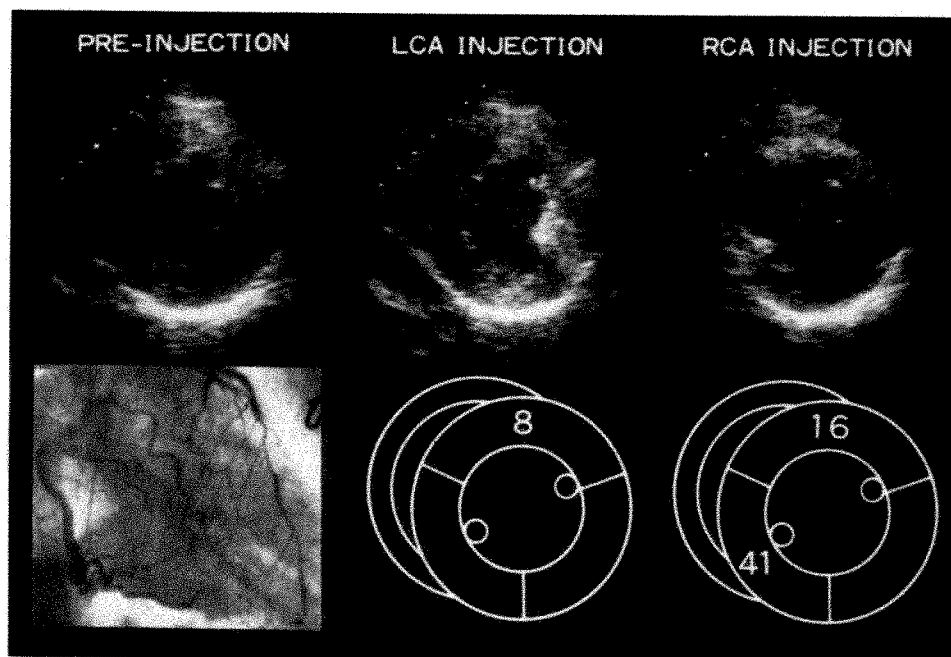


FIGURE 3. Myocardial contrast echocardiograms in a patient with anteroapical infarction with poor myocardial contrast staining despite good collaterals. Arrangement of panels are the same as Figure 1. The gain settings in preinjection image were adjusted to minimum so that contrast enhancement after injection of the contrast agent is visualized more clearly. Anteroapical region shows contrast enhancement only in the subepicardial myocardium during right coronary artery (RCA) injection. Left ventriculography shows akinetic wall motion in the anteroapical region. LCA = left coronary artery.

these discrepant cases, the area perfused with collateral vessels was proven to be akinetic or dyskinetic by left ventriculography, suggesting that the coronary collateral vessels in these patients may not be active enough to preserve the wall motion. This finding was consistent with the previous report in which meaningless collaterals from the view of the myocardial salvage were observed in thallium scintigraphic study.¹⁸

In this study, contrast enhancement was observed in the subepicardium in patients with severe asynergy despite good collateral vessels. Piek and Becker²⁰ found that collateral vessels play an important role in determining infarct type, i.e., transmural versus subendocardial. Hiral et al²¹ showed a beneficial effect of the collaterals on the prevention of LV aneurysm formation. Thus, contrast enhancement in the subepicardium in patients with severe asynergy might still be beneficial in keeping wall motion abnormalities minimum.

Methodologic limitations of the study: In this study, hand-agitated amidotrizoate sodium meglumine was used as a contrast agent. This method of agitation inherently has limitations in the quantification of contrast enhancement as discussed previously.¹²

Enhancement of gray level is affected by several factors, such as gain setting, angle of incidence, axial and

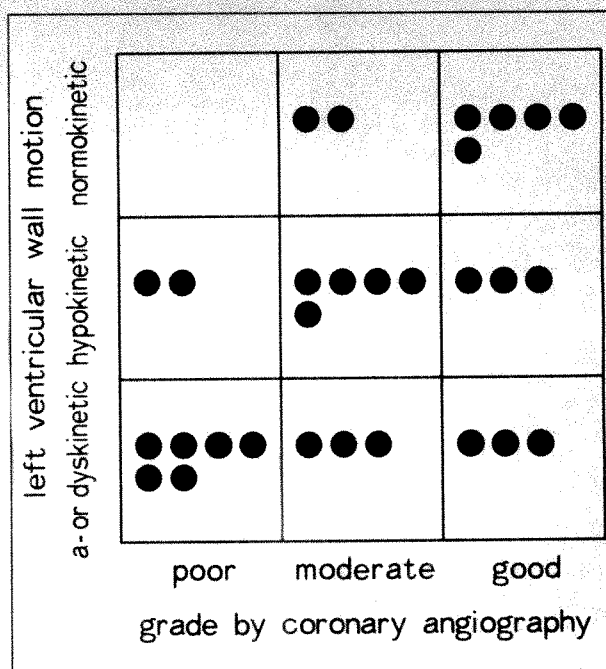


FIGURE 4. Relation between the grade of collateral vessels obtained with coronary angiography and degree of left ventricular wall motion abnormalities.

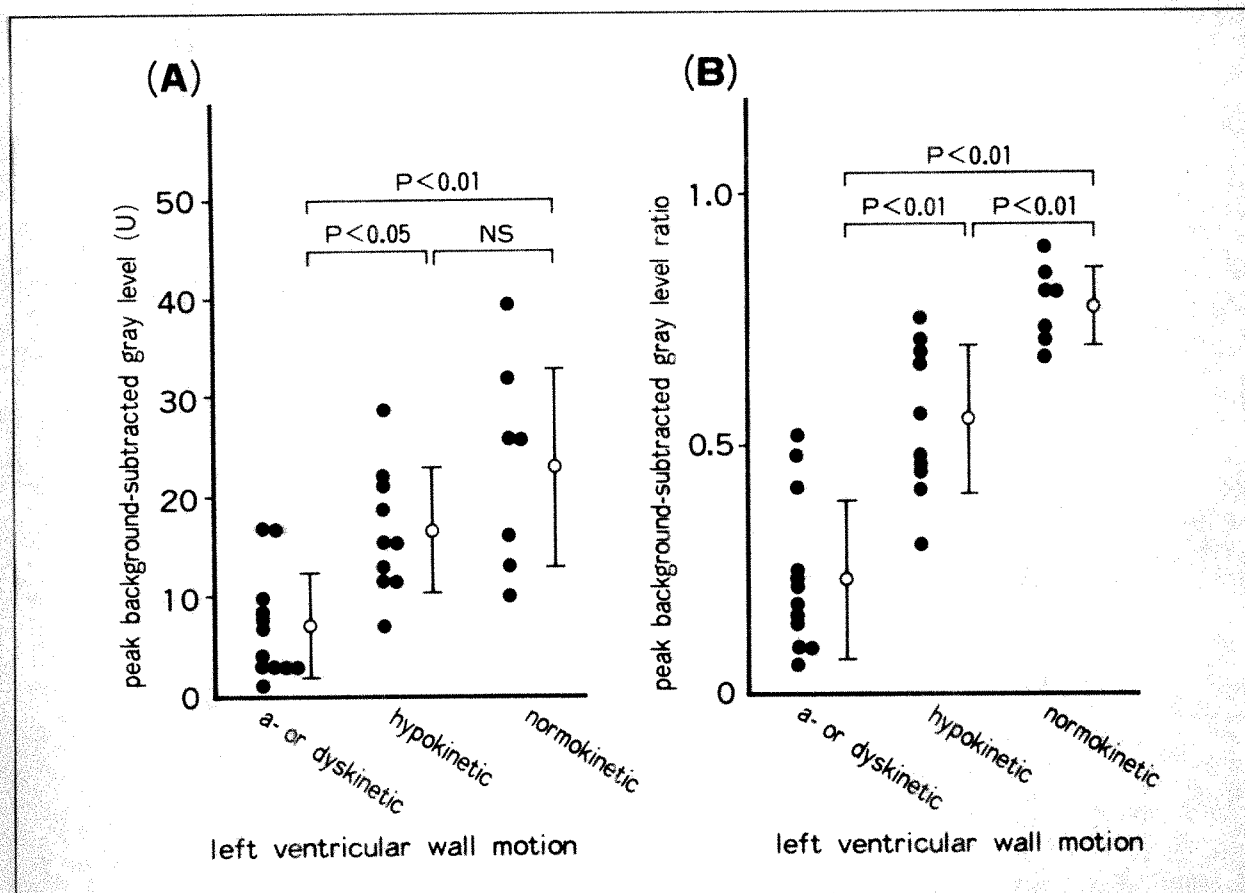


FIGURE 5. Relation between myocardial contrast echocardiographic parameters and left ventricular wall motion abnormalities. Peak background-subtracted gray level (PGL) in the infarct area during the donor artery (noninfarct) injection (A) and PGL ratio of the infarct to noninfarct areas (B) were higher as left ventricular wall motion was better. These myocardial contrast echocardiographic parameters were lower in the akinetic (a-) or dyskinetic group than in the hypokinetic or normokinetic groups. PGL ratio was significantly lower in the hypokinetic than in the normokinetic group. NS = not significant.

lateral resolution, the ultrasound attenuation and the injection volume and speed of contrast agent. Therefore, there are significant limitations in the measurements of absolute myocardial blood flow. Patients with posterolateral old myocardial infarction were omitted from this study because the posterolateral region obviously has poor resolution in contrast echo image. We corrected PGL in the infarct area for that in the noninfarct area to reduce the variability of gray level. However, there are unavoidable slight differences in the gray level depending on the depth of region of interest, and therefore this correction was not perfect.

Finally, the 2-dimensional echocardiographic short-axis image of the myocardium was divided into only 3 segments along the common coronary artery perfusion boundaries by the operator. Therefore, there should be potential variants of perfusion patterns, if dominant vessel and coronary variants are considered.

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Morphometric Analysis of the Composition of Coronary Arterial Plaques in Isolated Unstable Angina Pectoris with Pain at Rest

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Coronary artery plaque morphology was studied in 354 five-mm segments of the 4 major (left main, left anterior descending, left circumflex and right) epicardial coronary arteries in 10 patients with isolated unstable angina pectoris with pain at rest. The 4 major coronary arteries were sectioned at 5-mm intervals and a drawing of each of the resulting 354 Movat-stained histologic sections was analyzed using a computerized morphometry system. The major component of plaque was a combination of dense acellular and cellular fibrous tissue with much smaller portions of plaque being composed of pultaceous debris, calcium, foam cells with and without inflammatory infiltrates and inflammatory infiltrates without foam cells. There were no differences in plaque composition among any of the 4 major epicardial coronary arteries. Plaque composition varied as a function of the degree of luminal narrowing. Linear increases were observed in the mean percent of dense fibrous tissue (from 5 to 50%), calcific deposits (from 1 to 10%), pultaceous debris (from 0 to 10%) and inflammatory infiltrates without significant numbers of foam cells (from 0 to 5%), and a linear decrease was observed in the mean percent of cellular fibrous tissue (from 94 to 22%) in sections narrowed up to 25% to more than 95% in cross-sectional area. Multiluminal channels were seen in all 10 patients (28 [19%] of the 146 sections narrowed >75% in cross-sectional area and in 36 [10%] of all 354 segments); occlusive thrombi in no patient; nonocclusive thrombi in 2 patients (1 section each of 2 arteries); plaque rupture in 2 patients (4 segments from 2 arteries); and plaque hemorrhages in 6 patients (11 sections from 10 arteries).

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Since the early 1970s several angiographic and morphologic studies have described the degrees of luminal narrowing of the major epicardial coronary arteries, some acute lesions in the coronary arteries, and the status of the left ventricular myocardium in patients with unstable angina pectoris.¹⁻⁴ No previous studies, however, have described the composition of coronary arterial atherosclerotic plaques in patients with unstable angina pectoris shortly before death. Such was the purpose of the present study. The focus is on the composition of the plaques, not the types and frequency of acute lesions in the coronary arteries. We examined, in a quantitative fashion, the components of coronary arterial plaques in each of 354 five-mm segments of the 4 major (left main, left anterior descending, left circumflex and right) epicardial coronary arteries in 10 patients with isolated angina pectoris with pain at rest.

METHODS

The autopsy records of the Pathology Branch of the National Heart, Lung, and Blood Institute were searched for cases coded as unstable angina pectoris. Patients were selected with isolated unstable angina at rest. All patients had unstable angina pectoris as recently defined by Braunwald.⁵ Cases were excluded in whom unstable angina developed in the presence of an aggravating extracardiac condition. Cases were excluded when death occurred during or immediately after cardiac catheterization or when coronary artery bypass surgery or percutaneous coronary angioplasty had been performed or thrombolytic therapy administered. Cases were selected in whom death occurred during or immediately after a hospital admission for evaluation of unstable angina and in whom there was no gross or microscopic evidence at necropsy of either transmural left ventricular necrosis or fibrosis.

The 4 major epicardial coronary arteries were excised intact from the heart, decalcified (if necessary), sectioned transversely at 5-mm intervals and labelled sequentially. The 5-mm segments then were decalcified again (if necessary), dehydrated in alcohols, cleared in xylene, embedded in paraffin and two 5-micron-thick sections were prepared from each segment. One section was stained by the Movat method,⁶ and 1 by hematoxylin and eosin.

The Movat stained sections were placed on the stage of a projection microscope. Using a 40X objective, the image was enlarged and a tracing of the artery was made on opaque white paper. The following areas were

outlined: potential lumen (total area outlined by the internal elastic membrane), residual lumen (potential lumen minus area of atherosclerotic plaque) and luminal thrombus (platelets, fibrin, erythrocytes and leukocytes). Components of plaque identified and outlined included dense fibrous tissue, loose fibrous tissue, cellular fibrous tissue, heavily calcified tissue, pultaceous debris, foam cells with and without lymphocytes, and inflammatory infiltrates without significant numbers of foam cells.

Definitions and descriptions of the various components of plaque were the following: *dense fibrous tissue* was an area of relatively acellular tissue composed primarily of dense collagen fibers; *loose fibrous tissue* was a relatively acellular, more delicate arrangement of collagen fibers; *cellular fibrous tissue* was composed of spindle cells resembling myofibroblasts, smooth muscle cells or fibroblasts admixed with collagen or elastic fibers, or a combination of these; *calcific deposits* were detected by red-brown granular staining areas (only solid heavily calcified areas were included in the analysis); *pultaceous debris* (presumably rich in extracellular lipid) were pale staining areas composed of amorphous material with abundant cholesterol clefts; *foam-cell aggregates* were composed of collections of plump, rounded, finely vacuolated cells; *foam cells and lymphocytes* were areas containing round, finely vacuolated or granular cells admixed with lymphocytes; *inflammatory in-*

filtrates without foam cells were isolated aggregates of lymphocytes and other inflammatory cells that were almost always seen surrounding small vascular channels. All areas were initially recognized with the projection microscope and confirmed by standard light microscopy.

After a labeled drawing of each section was made, the area of potential and residual lumens and the area of each component was determined using a computerized morphometry system. The individual areas were traced using a GTCO Micro Digi-Pad® and the area calculated using Macmeasure,⁷ a morphometric software package used in conjunction with a Macintosh SE® computer. The area of each component was then converted to a percentage of the total plaque area. Intraluminal thrombus was not considered to represent a component of plaque. Inter- and intraobserver variability using this method has been previously shown to be good.⁸

The percent luminal narrowing was determined by using the following formula: percent luminal narrowing = $(1 - \text{residual lumen area} / \text{potential lumen area}) \times 100$. The degrees of cross-sectional area luminal narrowing were then categorized into 5 groups: 0 to 25%, 26 to 50%, 51 to 75%, 76 to 95% and 96 to 100%. The results were verified by visual inspection of the section. If the outer circumference of the artery was not rounded and if the percent luminal narrowing appeared to have been

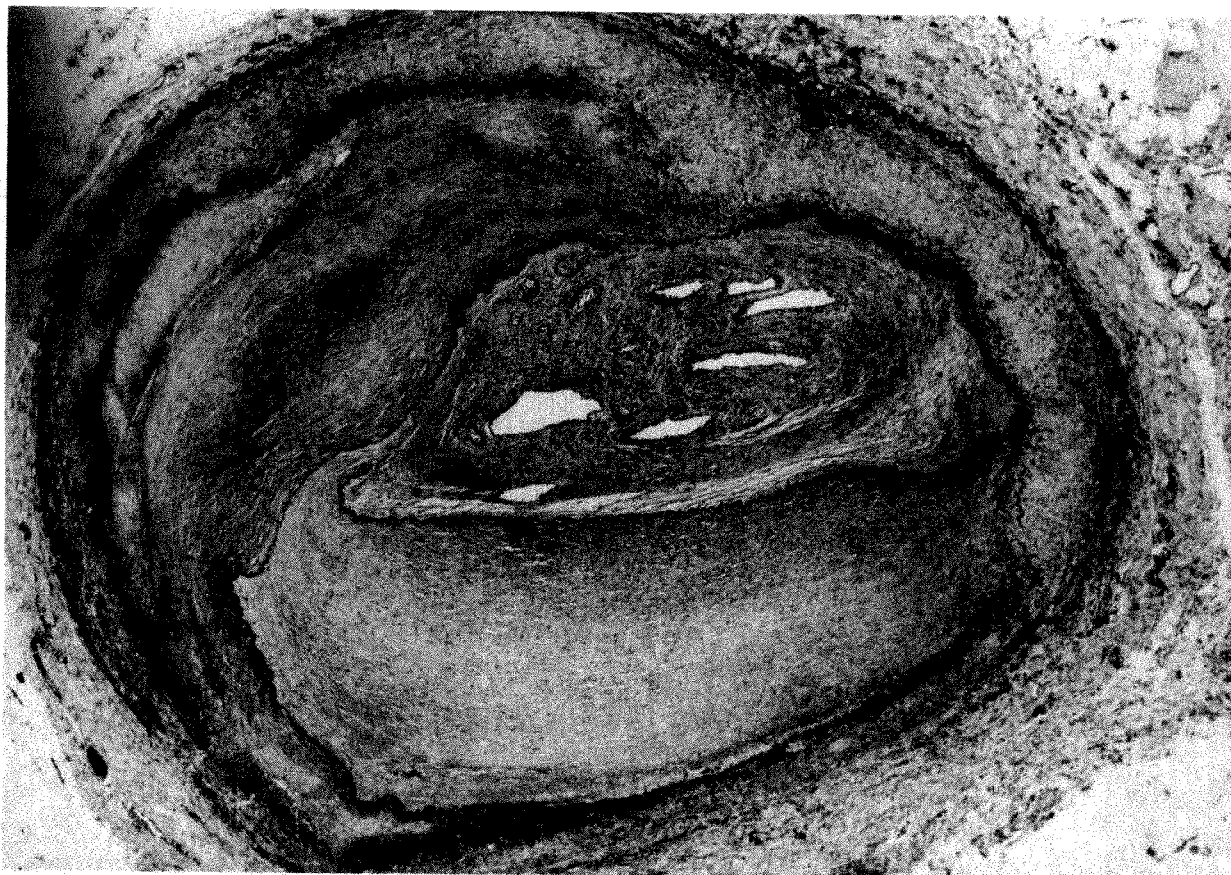


FIGURE 1. Photomicrograph of a Movat stained section of coronary artery that is severely narrowed by atherosclerotic plaque. The plaque is composed almost entirely of fibrous tissue and contains multiluminal channels. (Original magnification $\times 30$.)

TABLE I Degrees of Luminal Narrowing in 10 Patients with Unstable Angina Pectoris

Case	Age (yrs)	Number (%) of Segments with a Given Degree of Cross-Sectional-Area Narrowing				
		0-25%	26-50%	51-75%	75-95%	96-100%
1	47	1 (3)	6(18)	10(29)	14(41)	3 (9)
2	48	2 (4)	10(20)	12(23)	23(45)	4 (8)
3	49	8(22)	13(35)	9(24)	4(11)	3 (8)
4	51	0 (0)	0 (0)	12(43)	16(57)	0 (0)
5	58	0 (0)	14(28)	18(36)	10(20)	8(16)
6	65	0 (0)	7(21)	16(49)	8(24)	2 (5)
7	68	4(10)	5(13)	18(46)	9(23)	3 (8)
8	68	3(10)	8(29)	7(25)	8(29)	2 (7)
9	68	0 (0)	1 (4)	6(21)	14(50)	7(25)
10	70	0 (0)	12(46)	6(23)	8(31)	0 (0)
Total		18 (5)	76(22)	114(32)	114(32)	32 (9)

overestimated by this formula then the estimate obtained by visual inspection alone was used. The presence or absence of plaque rupture (a tear extending from the plaque's luminal surface into its substance), plaque hemorrhage, centrally located multiluminal channels (Figure 1) and thrombus was noted in each 5-mm segment.

Statistical methods: The mean percent of each component of plaque in the 4 major epicardial coronary arteries was determined by calculating a mean for each patient and averaging over individual persons, and adjusting for different distributions of luminal narrowing. An analysis of variance was used to assess the association between the percent composition of a given component and the specific artery of origin. In each analysis, the individual patient was the unit of study⁹; all calculations were performed using SAS.¹⁰

The analysis of plaque composition within each of the 5 categories of narrowing was performed by deter-

mining the mean composition for each patient of all segments within each of the 5 categories and averaging over individuals using analysis of variance model. A linear contrast model was used to assess whether a linear trend existed in the mean percent of any of the components over the 5 categories of narrowing. To correct for the fact that 8 correlated significance tests were performed, Bonferroni adjustments were used.¹¹

The analysis of plaque composition in segments of artery containing thrombus, hemorrhage, rupture or multiluminal channels was performed by calculating a mean for each component, averaging over individuals and adjusting for varying degrees in luminal narrowing. F tests were then used to compare the composition of segments with and without a given characteristic.

RESULTS

Clinical features: The 10 patients ranged in age from 47 to 70 years (mean 59). Only 1 patient (no. 8, Table I) was a woman. The duration of angina in the 9 patients in whom it was known ranged from 6 weeks to 19 years. All 10 patients had angina at rest during at least their last 48 hours of life and, additionally, the angina either had increased in frequency or the amount of stress required to elicit it had diminished during their last 2 months of life. Nine patients died during an admission to the hospital for the evaluation of angina, and the other patient died outside the hospital 9 days after hospitalization for unstable angina. At necropsy, none had gross or microscopic evidence of transmural (involvement of greater than the inner one half of the left ventricular wall) left ventricular necrosis. In 7 patients non-transmural left ventricular scars were present. The hearts ranged in weight from 330 to 540 g (mean 458).

Five-mm segments studied: Of 449 five-mm sections of coronary artery prepared, 95 were excluded from analysis because they contained either branch points or sectioning artifacts such that the entire cross-

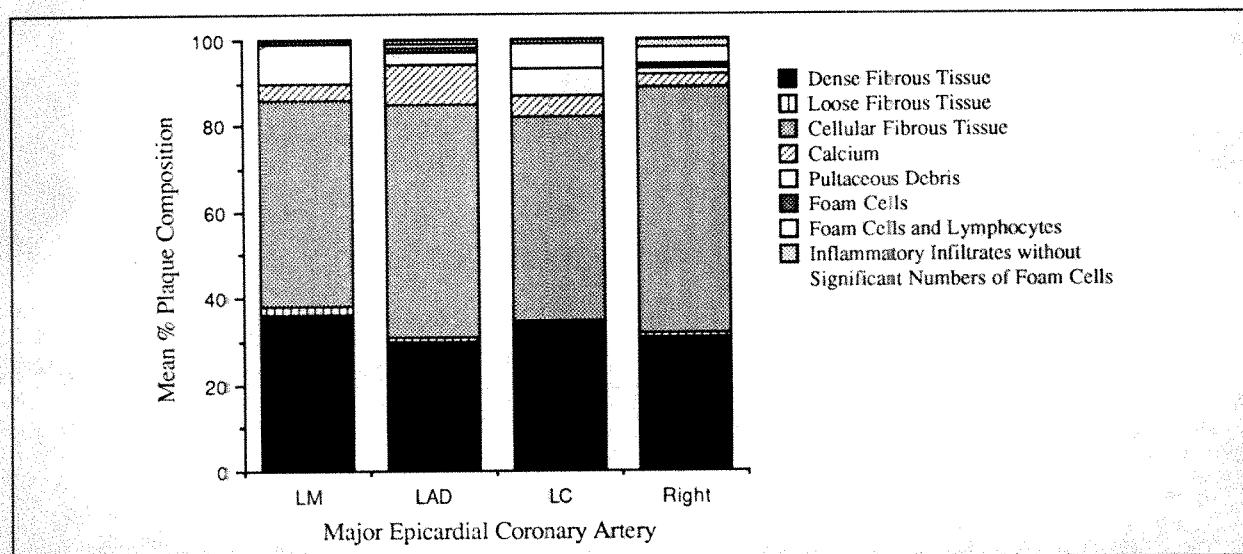


FIGURE 2. Mean percent plaque composition in each of the 4 major epicardial coronary arteries. LAD = left anterior descending; LC = left circumflex; LM = left main.

TABLE II Mean Percent of Various Components of Plaque in Each of the Five Categories of Narrowing

	0-25% mean (SE) (n = 5)	26-50% mean (SE) (n = 9)	51-75% mean (SE) (n = 10)	76-95% mean (SE) (n = 10)	96-100% mean (SE) (n = 8)	Normal p for Linear Trend
Dense fibrous tissue	5(5)	23(3)	39(3)	42(3)	50(3)	0.0001*
Loose fibrous tissue	0(1)	2(1)	2(1)	1(1)	1(2)	0.25
Cellular fibrous tissue	94(6)	66(4)	41(4)	30(4)	22(5)	0.0001*
Heavily calcified tissue	1(2)	0(2)	7(2)	9(2)	10(2)	0.0002†
Pultaceous debris	0(2)	0(2)	2(2)	8(2)	10(2)	0.0001*
Foam cells	0(1)	1(1)	1(1)	1(1)	1(1)	0.45
Foam cells and lymphocytes	0(3)	8(2)	7(2)	8(2)	2(2)	0.31
Inflammatory infiltrates without significant numbers of foam cells	0(2)	0(1)	1(1)	1(1)	4(1)	0.005‡

n = number of cases from which the mean was calculated (5 cases had no sections narrowed <25%, 1 had no sections narrowed 26-50% and 2 had no sections narrowed 96-100%).
* = Bonferroni p < 0.001; † = Bonferroni p < 0.01; ‡ = Bonferroni p < 0.05.

sectional area could not be studied. The remaining 354 sections (an average of 35/case) were studied in detail.

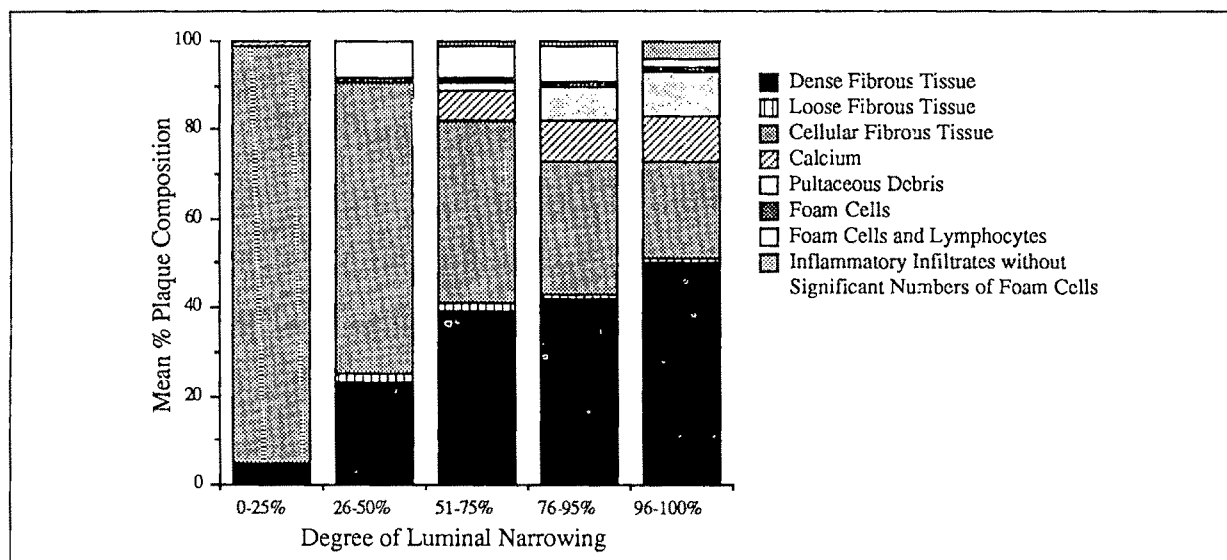
Amounts of coronary narrowing: The degrees of luminal narrowing in each case are listed in Table I. All cases had severe (>75% decrease in cross-sectional area) narrowing of ≥ 1 of the 4 major epicardial coronary arteries by plaque. Nine had >75% cross-sectional area narrowing of the left anterior descending, left circumflex and right coronary arteries by plaque, and 4 had this degree of narrowing of all 4 major epicardial coronary arteries. Segments narrowed >95% in cross-sectional area were present in 8 of the 10 patients. The percent or segments narrowed >75% cross-sectional area in each case ranged from 19 to 75% (mean 41%).

Atherosclerotic plaque composition: The mean compositions of plaque, corrected for varying degrees of luminal narrowing, of the 4 major epicardial coronary arteries are detailed in Figure 2. In each of the 4 arteries, the major component of plaque was a combination of dense and cellular fibrous tissue. Smaller amounts of loose fibrous tissue, pultaceous debris, calcium, foam cells with and without inflammatory infiltrates and in-

flammatory infiltrates without foam cells were present. The mean percent of any given component was similar in each of the 4 major coronary arteries.

The mean composition of plaque, analyzed in each of the 5 categories of luminal narrowing, is detailed in Table II and in Figure 3. Linear increases in the mean percent of dense fibrous tissue (from 5 to 50%, Bonferroni p < 0.001), calcium (from 1 to 10%, Bonferroni p < 0.01), pultaceous debris (from 0 to 10%, Bonferroni p < 0.001), and lymphocytes without foam cells (from 0 to 5%, Bonferroni p < 0.05) occurred across the 5 categories of narrowing. The mean percent of cellular fibrous tissue decreased across the 5 categories from 94 to 22% (Bonferroni p < 0.001).

Intraluminal coronary thrombus: Minute intraluminal thrombi were seen in 2 sections, 1 from each of 2 patients. In both cases, the thrombus was nonocclusive and composed of platelets and fibrin. Both thrombi were located in segments narrowed >75% in cross-sectional area by plaque and neither was associated with underlying plaque hemorrhage or rupture. The mean percent of plaque occupied by foam cell aggregates was

**FIGURE 3.** Mean percent plaque composition in each of the 5 categories of cross-sectional-area narrowing.

significantly greater (5 vs 1%, $p = 0.04$) in the 2 sections containing thrombus compared to the segments without thrombus.

Plaque rupture: This was seen in 4 sections from 2 patients. In each, both sections were from the same artery. In 1 case, both segments containing rupture were associated with hemorrhage into plaque. The composition of plaque in these sections was similar to that of sections without rupture.

Plaque hemorrhage: This was present in 11 sections from 10 arteries in 6 patients. The mean percents of pultaceous debris and loose fibrous tissue were greater (12 ± 3 vs 3 ± 2 , $p = 0.008$ and 9 ± 3 vs 1 ± 1 , $p = 0.04$, respectively) and the mean percent of dense fibrous tissue (21 ± 5 vs 32 ± 2 , $p = 0.04$) was less in sections with hemorrhage than in those without.

Multiluminal channels: These were identified in all 10 patients, in 28 (19%) of 146 sections narrowed >75% in cross-sectional area and in 36 (10%) of all of the 354 5-mm segments. Of the 36 segments containing >1 channel, the lumen was narrowed >75% in cross-sectional area in 28; from 51 to 75% in 6 and from 26 to 50% in 2. Sections of artery containing multiluminal channels contained a higher percent of dense acellular fibrous tissue (41 ± 4 vs $32 \pm 2\%$, $p = 0.03$) and less pultaceous debris (0.0 ± 1 vs 4 ± 1 , $p = 0.001$) than did sections without multiluminal channels.

DISCUSSION

Plaque composition: The findings in this study indicate that the major component of atherosclerotic plaques in the 4 major epicardial coronary arteries in patients with isolated unstable angina pectoris at rest is a combination of cellular and dense acellular fibrous tissue (82 to 88%). Pultaceous debris, calcium, loose fibrous tissue, inflammatory infiltrates, and foam cell aggregations made up much smaller portions of the plaques. Plaque composition was similar in each of the 4 major coronary arteries. Plaque composition changed as a function of the degree of luminal narrowing. The

mean percent of dense fibrous tissue, pultaceous debris, calcium and inflammatory infiltrates without foam cells increased and the amount of cellular fibrous tissue decreased in a linear fashion over the 5 categories of cross-sectional area narrowing.

While quantitative information on coronary arterial plaque composition is now available on other patients with fatal coronary artery disease—that is, acute myocardial infarction and sudden coronary death⁸—there is no previously published information on plaque composition in patients with clinically isolated unstable angina pectoris. The mean percent of the various components of plaque in 5-mm segments of coronary arteries narrowed >75% in cross-sectional area in these 3 groups of patients is shown in Figure 4. While the major component of plaque in all 3 groups is a combination of dense and cellular fibrous tissue, significant differences occur in the mean percent of plaque occupied by pultaceous debris. The mean percent of plaque occupied by pultaceous debris is about 8% in patients with angina pectoris at rest and sudden coronary death, conditions associated with a low frequency of occlusive intraluminal thrombi, and about 16% in patients with fatal acute myocardial infarction, a condition associated with a high frequency of intraluminal thrombi. Because occlusive thrombi usually overlie plaque rich in pultaceous debris,^{8,12-16} the differences in the mean percent of pultaceous debris in these subsets of patients with coronary artery disease may explain the differences in the frequency of intraluminal thrombi.

Multiluminal channels within atherosclerotic plaques: These were seen in every patient, in 19% of segments narrowed >75% in cross-sectional area and in 10% of all coronary segments. The segments with multiluminal channels contained significantly more dense fibrous tissue than did the segments without multiluminal channels but with a similar degree of luminal narrowing. If thrombi are injected into the lumens of systemic veins, the clots migrate to the lungs, and they often organize into fibrous plaques containing multiluminal

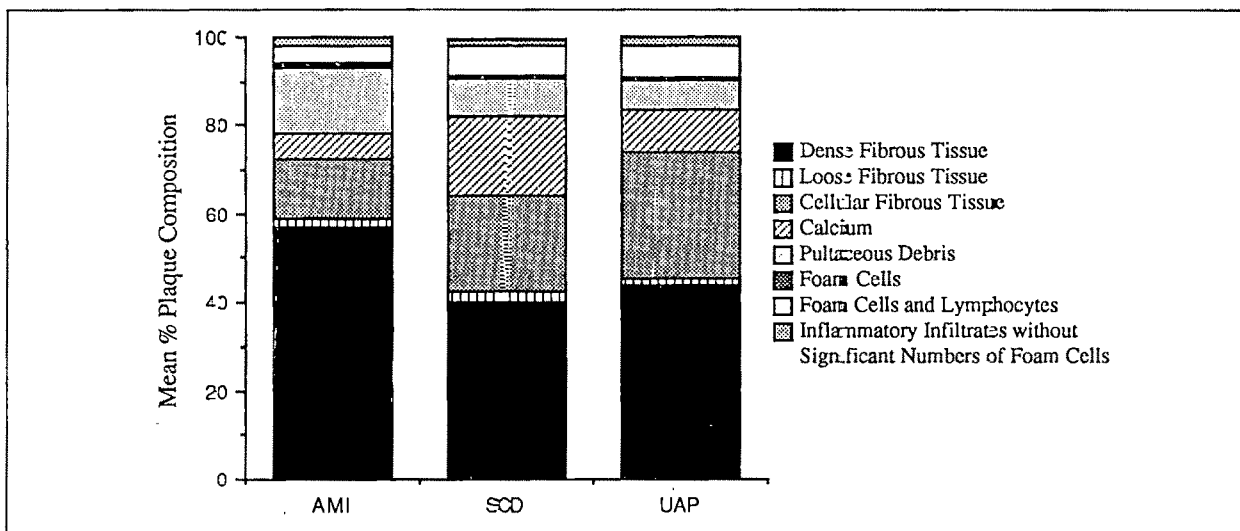


FIGURE 4. Mean percent plaque composition of sections of coronary artery narrowed >75% in cross-sectional area. AMI = acute myocardial infarction; SCD = sudden coronary death without left ventricular necrosis; UAP = unstable angina pectoris.

channels.¹⁷ This fact suggests that arteries containing multiluminal channels are the result of organization of thrombi. It is therefore likely that a large portion of the plaque in the 19% of segments narrowed >75% in cross-sectional area is due to the organization of thrombi into fibrous plaques containing multiluminal channels.

The frequency of segments of coronary artery containing multiluminal channels in patients with isolated unstable angina pectoris has not been noted in other studies. Levin and Fallon¹⁸ compared postmortem angiographic and histologic findings in patients with fatal coronary artery disease of various types. They demonstrated that angiographic narrowings with either irregular borders or intraluminal lucencies by histologic examination consisted of a variety of lesions including "recanalized thrombi," nonocclusive thrombi, plaque hemorrhage or plaque rupture. While narrowings containing recanalized thrombi were not illustrated, presumably they contained multiluminal channels. Narrowings with a similar angiographic appearance (eccentric lumens with irregular or overhanging borders) were observed by Ambrose et al¹⁹ in 50 of 92 narrowings in 63 patients with unstable angina pectoris and in only 4 of 55 narrowings in 47 patients with stable angina pectoris. While histologic evaluation of these narrowings, which they believed were characteristic of patients with unstable angina, was not possible, they attributed the angiographic appearances to the presence of either plaque rupture or intraluminal thrombi. We found plaque rupture in only 2 of our 10 patients and nonocclusive intraluminal thrombi in only 2 of our 10 patients. In contrast, multiluminal channels were observed in all 10 patients. While coronary angiography of the epicardial coronary arteries was not available for comparison in the 10 patients we studied, it is likely that a great proportion of the narrowings would have been due to plaque containing multiluminal channels.

Limitations: Identification of calcium in formalin fixed partly decalcified tissue may result in an underestimation of the total mean percent of calcium. Likewise, processing of tissues in xylenes prevented us from using specific lipid stains and hence the total amount of lipid may be underestimated.

In summary, the major component of plaque in patients with unstable angina is fibrous tissue. Multiluminal channels, a finding suggesting the earlier pres-

ence of thrombus that organized, was present in all patients and in 10% of the segments studied. Plaque rupture was seen in 2 patients, nonocclusive thrombi were seen in 2 patients, and plaque hemorrhage in 6 of the 10 cases. The zero frequency of occlusive thrombi at necropsy might be explained in part by the low mean percent of pultaceous debris in the 4 major epicardial coronary arteries.

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Relation of Peri-Infarction Block to Ventricular Late Potentials in Patients with Inferior Wall Myocardial Infarction

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This study explores the relation of the presence of peri-infarction block to ventricular late potentials in patients with inferior wall myocardial infarction (MI). The hypothesis was that both the gross peri-infarction block pattern and subtle low-level ventricular late potentials are expressions of conduction abnormality associated with infarction. The consequent question arose whether peri-infarction block may have the same association with sustained ventricular arrhythmias that has been demonstrated in postinfarction patients with ventricular late potentials. Seventy patients with documented Q-wave MI were divided into those with (23) and those without (47) peri-infarction block. Signal-averaged electrocardiograms were obtained. Analysis of the vectormagnitude complex revealed that the total duration of that complex and the duration of terminal potential under $40\mu\text{V}$ in the peri-infarction group exceeded that in the group without peri-infarction block ($p < 0.0001$). The voltage in the last 40 ms of the vectormagnitude complex was also significantly less in the peri-infarction group ($p < 0.0005$). There were 13 instances of sustained ventricular tachycardia, ventricular fibrillation or sudden death occurring subsequent to infarction not associated with the acute ischemic event, 11 of which occurred in the peri-infarction group. The significantly higher incidence of late potentials along with the significantly higher incidence of sustained ventricular arrhythmias in the peri-infarction group suggests that the presence of peri-infarction block on the surface electrocardiogram may provide another marker for identifying persons at increased risk for these arrhythmias subsequent to MI.

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Scherlag et al,¹ in an editorial in 1985, suggested the possibility of a relation between peri-infarction block and ventricular late potentials. That editorial provided the impetus for this investigation.¹ Our purpose in this work was to evaluate this thesis and to explore the relation of peri-infarction block and the occurrence of sustained ventricular arrhythmias.

The term peri-infarction block was suggested by W. T. McCollum, MD, as acknowledged by First et al² in the latter group's initial publication in 1950. These writers used a set of criteria for peri-infarction block that included the requirement that QRS complexes be ≥ 0.11 second. They recognized, although they did not emphasize, that in electrocardiographic zones remote from the infarction the QRS duration could be within normal limits. In 1954, Grant et al³ used an altered definition, stating that, in the case of inferior wall myocardial infarction (MI), the terminal 0.04-second forces may be expected to be directed inferiorly and rightward, while the initial forces or the Q wave would, as expected, be directed away from the infarcted zone.

First et al² had been motivated by the work of Wilson et al,^{4,5} who had emphasized the importance of intraventricular block. Unfortunately, in Grant's otherwise helpful work, the concept of peri-infarction block was further altered in the mid-1950s to the early 1970s to include instances of left anterior fascicular block.^{3,6-9} Describing the concept of the hemiblocks, Rosenbaum et al¹⁰ rightly concluded that the term peri-infarction block had been applied inappropriately to instances of ventricular conduction abnormalities specific to the left anterior fascicle.

The anatomic basis for peri-infarction block was suggested by First et al² describing direct recordings from infarcted myocardium. Over the center of the infarction they depicted a QS pattern; when the exploring electrode was moved more peripherally over the peri-infarct zone, late activation could be demonstrated. The electrocardiographic complex, then, demonstrated an initial Q wave followed by a broad R wave, the downstroke of which was slurred and terminated a relatively prolonged QRS interval.

As early as 1961, investigators observed fragmented electrical activity after the dominant cardiac deflection in certain pathological states.¹¹ It was later specifically recognized that such activity was associated with ventricular arrhythmias, as these fractionated potentials were recorded (usually during sinus rhythm) from endocardial, epicardial and intramural locations under con-

ditions of ischemia or infarction¹²⁻²² associated with ventricular tachycardia; fragmented local activity was also recorded by Josephson et al²³ in man using catheter electrodes placed near the periphery of an aneurysm.

By means of signal averaging for reduction of noise from electrical interference, abnormal potentials after the QRS were recorded from the body surface of experimentally infarcted dogs^{22,24} as well as from patients after MI who developed sustained ventricular tachycardia.²⁵⁻²⁸ An abundance of reports have followed these initial studies confirming the value of low-level signals in patients after MI in predicting those at increased risk for ventricular tachycardia or sudden death.²⁹⁻³⁸ Against this background we proceeded with the present work.

METHODS

The standard 12-lead electrocardiogram and signal-averaged electrocardiogram (SAECG) were evaluated in 70 patients (ages 25 to 77 years) with clinically and electrocardiographically documented Q-wave inferior wall MI over a 2-year period at the Medical College Hospital and its associated Veterans Administration Medical Center. All patients had Q waves in at least 2 inferior leads that exceeded 30 ms. None had QRS complexes in the extremity leads other than II, III and aVF in excess of 100 ms, i.e., no instances of bundle branch block or other intraventricular conduction defects were included. Patients with diagnostic Q waves in other electrocardiographic infarct zones were not included. Our effort, then, was to study a group with simi-

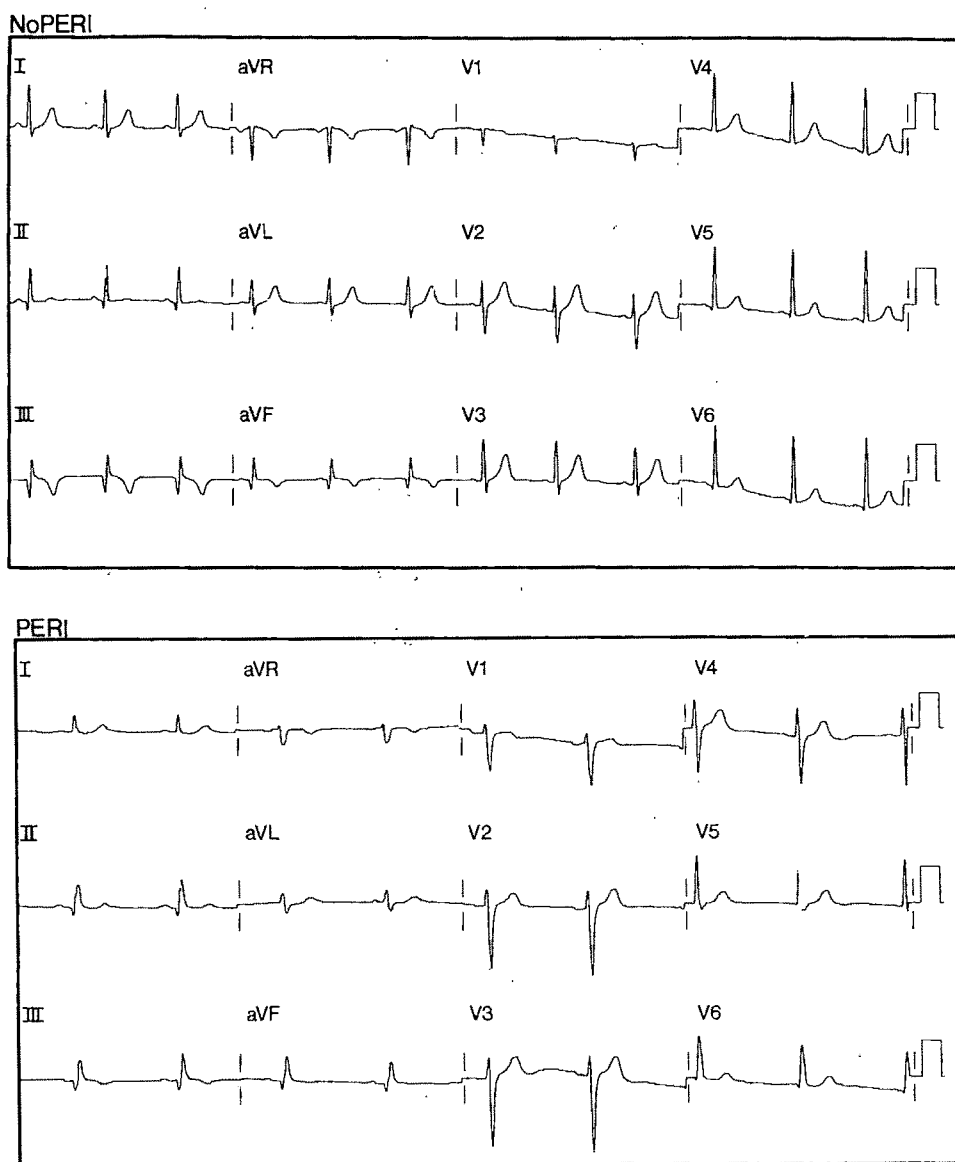


FIGURE 1. Standard 12-lead electrocardiogram of a patient without peri-infarction block (NoPERI) compared to that of a patient with peri-infarction block (PERI). In the NoPERI patient, QRS duration of the extremity leads was 90 ms. Note the sharp descending limb of the R wave in the inferior leads (II, III and aVF). In the PERI patient, QRS duration of leads II, III and aVF was 110 to 120 ms. Note the relatively normal QRS duration of 80 ms in lead I complex compared to the wider complexes in the inferior leads (II, III and aVF). Note also the slurs on the descending limb of the R wave in these same leads. The calibration signal is $1 \mu\text{V} \times 240 \text{ ms}$.

lar, relatively localized MIs, without the confounding effects of generalized conduction defects or multiple site MIs. At present, 63 of the patients are alive, 4 are deceased and 3 were followed briefly, but have now been lost to follow-up.

The patients were divided into 2 groups, those with peri-infarction block and those without peri-infarction block. For the purposes of this study, peri-infarction block was defined as being present when the following criteria were met: (1) the QRS duration in leads II and aVF exceeded by at least 20 ms the QRS duration in lead I; (2) Q waves in 2 or more inferior leads exceeded 30 ms; and (3) the Q waves in leads II, III or aVF were followed by an R wave, the downstroke of which was slurred and terminated the relatively prolonged QRS. For criterion (1), 20 ms was chosen for 2 reasons. First, it provided a sufficient increase in QRS duration (in a lead in the infarct zone compared with the non-infarct zone) to clearly suggest regionally altered conduction properties. Secondly, this value permitted consistent reproduction of measurements at standard electrocardiographic paper speeds magnified 3 times. Lead I was chosen for specific comparison as the only other bipolar extremity lead, a lead in which the electrical axis is generally perpendicular to the direction of activation of the inferior wall, and, therefore, most likely to be insensitive to the infarct zone. Consequently, it was deemed likely to be representative of a normal or non-infarct-related zone. Meeting these criteria for peri-infarction block were 23 patients, while 47 patients were classified without peri-infarction block.

Standard electrocardiograms were obtained on a 3-channel recorder; SAECGs were obtained (after informed consent) on a high resolution acquisition system at least 1 week after infarction. Bipolar transverse (X), vertical (Y) and anterior-posterior (Z) leads were recorded in approximately orthogonal fashion using an ensemble of 200 repeating cycles. A noise level below 1

μV was required. Premature beats or those morphologically different from the predominant template were rejected. A bidirectional high-pass digital filter was used with the band pass of 25 to 250 Hz. A vectormagnitude complex was derived from the $\sqrt{X^2+Y^2+Z^2}$.²⁸ Measurements made on the signal-averaged and filtered vectormagnitude complex included the total duration, the duration of potential $<40 \mu\text{V}$ and the root mean square of the voltage of the last 40 ms. Based on our normal series these parameters were considered abnormal when the total duration of the vectormagnitude complex was $>120 \text{ ms}$, the duration of potential $<40 \mu\text{V}$ was $>39 \text{ ms}$ and the voltage of the last 40 ms was $<25 \mu\text{V}$.^{39,40}

Signal-averaged measurements are expressed as mean ± 1 standard deviation of the mean. Statistics were performed using the Student *t* test and chi square analyses.

Eight of these patients (6 with and 2 without peri-infarction block) with a history of syncope, presyncope and sustained ventricular arrhythmias were referred to us for electrophysiological study. Standard protocols were applied.⁴¹

RESULTS

Figure 1 shows the electrocardiogram of a patient without peri-infarction block compared with that of a patient with peri-infarction block. Figure 2 shows a magnified lead II complex from each electrocardiogram. In the patient without peri-infarction block, the QRS durations of the inferior leads (II, III and aVF) are approximately equal to the duration of lead I; also, the R wave in the inferior leads has a sharp descent. In the electrocardiogram of the patient with peri-infarction block, however, all criteria are fulfilled. The QRS duration of lead I is relatively normal, while the QRS durations in all inferior leads exceed that in lead I by at least 20 ms and the Q wave in lead II exceeds 40 ms. Note especially the slowed or slurred descending limb of the

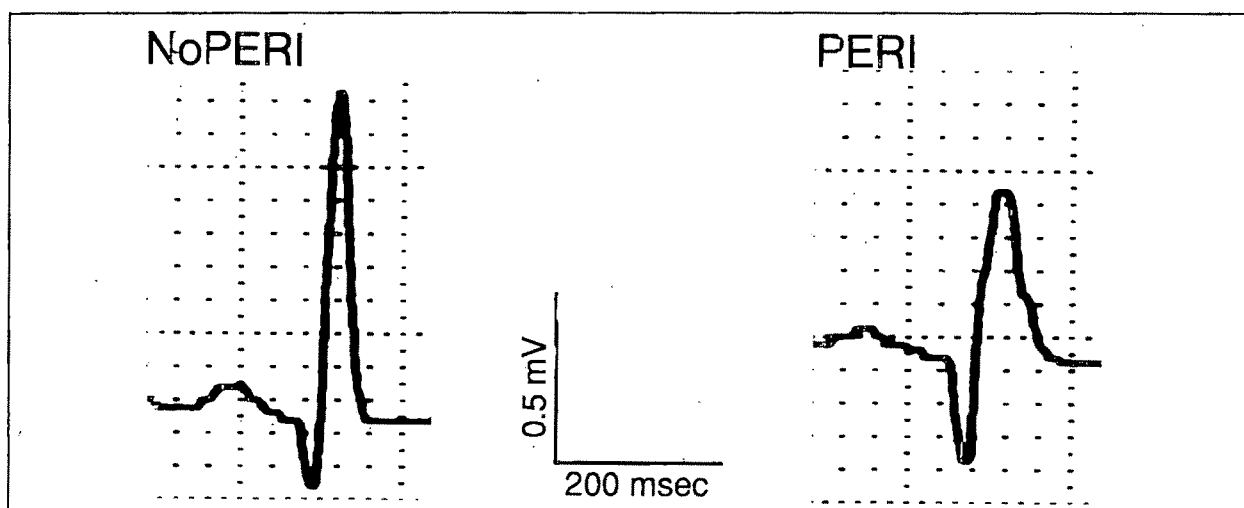


FIGURE 2. An enlarged lead II complex from each electrocardiogram shown in Figure 1. Note the contrast between the sharpness of the descending limb of the R wave in the patient without peri-infarction block (NoPERI) and the slurred descent of the R wave in the patient with peri-infarction block (PERI).

R wave in the inferior leads. These comparisons can best be appreciated in Figure 2. The amplified and averaged Y lead of the orthogonal set from the SAECG was also viewed for enhancement and confirmation of detail of the peri-infarction morphology.

Table I lists the signal-averaged parameters determined for each group of patients. There were no statistical differences in age of the 2 groups. Total duration of the vectormagnitude complex and duration of potential $<40 \mu\text{V}$ in the peri-infarction group exceeded that in the group without peri-infarction block ($p < 0.0001$); the voltage of the last 40 ms was less in the peri-infarction group than in the group without peri-infarction block ($p < 0.0005$). The separation of the peri-infarction patients from those without peri-infarction block can be visually appreciated on the 3-dimensional perspective graph plot (Figure 3). The squares, representing the peri-infarction patients, tend to cluster toward the ends of the axes, reflecting the longer vectormagnitude complex duration and the longer duration of potential $<40 \mu\text{V}$, while their short stems reflect the low amplitude of the voltage of the last 40 ms of their SAECG. Conversely, the patients without peri-infarction block (circles) cluster in the corner of the diagram toward the ends of the axes representing the shorter vectormagni-

TABLE I Signal-Averaged Electrocardiographic Parameters in Patients With and Without Peri-Infarction Block

	NoPERI	PERI	p Value
No. of pts	47	23	
Age (yrs)	54 ± 11	58 ± 10	NS
SAECG			
VMCd (ms)	102 ± 11	133 ± 17	<0.0001
LASd (ms)	23 ± 9	40 ± 17	<0.0001
V40 RMS ($\mu\text{V RMS}$)	71 ± 63	20 ± 12	<0.0005

NoPERI = without peri-infarction block; NS = not significant; PERI = with peri-infarction block; SAECH = signal-averaged electrocardiogram; VMCd = total duration of the vectormagnitude complex; LASd = duration of potential $<40 \mu\text{V}$; V40 RMS = root mean square voltage of the last 40 ms.

tude complex duration, the shorter duration of potential $<40 \mu\text{V}$ and the higher voltage found in the last 40 ms of their SAECH.

Figure 4 shows the SAECHs from the peri-infarction patient with ventricular tachycardia and the patient without peri-infarction block without ventricular tachycardia whose standard electrocardiograms appear in Figure 1. In the peri-infarction patient, there is terminal prolongation of low-level potential, increased duration of the total complex and very low amplitude of the last 40 ms. These findings contrast with the sharper descent

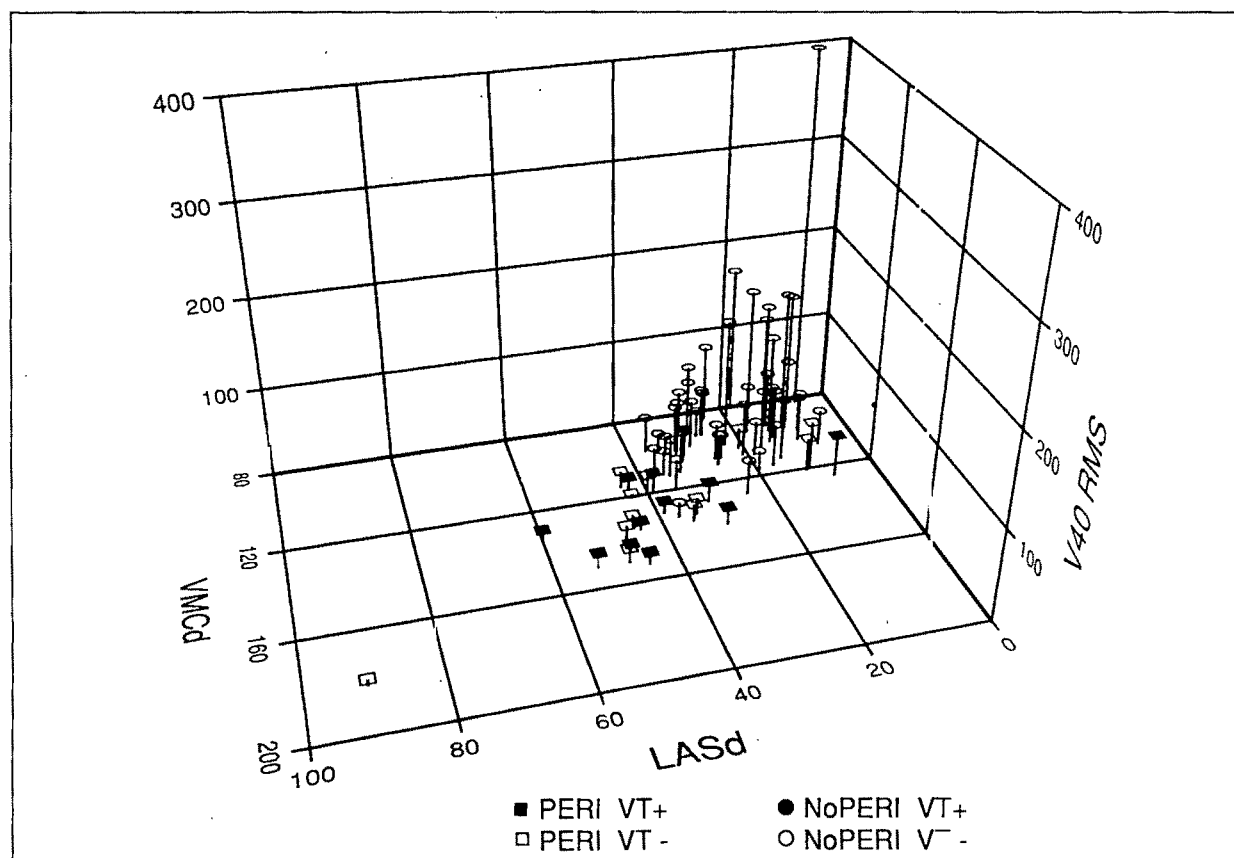


FIGURE 3. This 3-dimensional plot emphasizes the cluster of the patients with peri-infarction block (PERI, squares) toward the lower root-mean-square voltage in the last 40 ms (V40 RMS), the longer vectormagnitude complex (VMCd) and the longer low-amplitude signals under $40 \mu\text{V}$ (LAS 40). The patients without peri-infarction block (NoPERI, circles) cluster toward the higher values of V40 RMS, the lower values of VMCd and LASd. Solid symbols represent patients with sustained ventricular arrhythmias. See text for discussion.

TABLE II Occurrence of Abnormal Signal-Averaged Electrocardiographic Parameters in Patients With and Without Peri-Infarction Block

	NoPERI (n = 47)	PERI (n = 23)	P Value
Criterion of Abnormality (%)			
VMCd >120 ms	1 (2)	16 (70)	<0.0001
LASd >39 ms	0	13 (56)	<0.0001
V40 RMS <25 μ V RMS	4 (8)	19 (83)	<0.0001
No. Abnormal Parameters (%)			
0	43 (91)	1 (4)	<0.0001
1	3 (6)	4 (17)	NS
2	1 (2)	8 (35)	<0.001
3	0	10 (43)	<0.0001

Abbreviations as in Table I.

of terminal voltage level, the narrower complex and the relatively high amplitude of the terminal 40 ms from the patient without peri-infarction block.

There were 13 instances of sustained ventricular tachycardia, ventricular fibrillation or sudden death, 11 of which occurred in the group with peri-infarction block. This difference is highly significant ($p < 0.00005$). In the 2 patients without peri-infarction block with ventricular tachycardia, the SAECG criteria for positivity were absent. Thus, 96% of the patients with peri-infarction block had 1 or more abnormalities on the SAECG whereas only 8% of the group without

peri-infarction block had 1 or more abnormalities. It should be emphasized then that 47% of the peri-infarction group had sustained ventricular arrhythmias, while only 4% of the group without peri-infarction block demonstrated such arrhythmias.

Of the remaining 12 peri-infarction patients who have, as yet, not had sustained ventricular tachycardia or fibrillation, 11 had 1 or more positive criteria for an abnormal SAECG: 5 had 3 positive parameters, 4 had 2 positive parameters, 2 had 1 positive parameter and 1 had no positive parameters (Table II). Of the 8 patients studied in the electrophysiology laboratory, 5 of the 6 peri-infarction patients had inducible ventricular tachycardia. Neither of the 2 patients without peri-infarction block was inducible; 1 of these, however, had therapeutic levels of an antiarrhythmic agent at the time of study.

Thus, in the peri-infarction group, the most frequently abnormal SAECG parameter was the voltage magnitude of the last 40 ms ($<25 \mu$ V). When 1 or more positive criteria were required, ventricular late potentials in the peri-infarction group had a sensitivity of 100%, a specificity of 8%, a positive predictive value of 50% and a negative predictive value of 100%. In the group without peri-infarction block, the occurrence of ventricular late potentials had a sensitivity of 0%, a specificity of 91%, a positive predictive value of 0% and a negative predictive value of 95%.

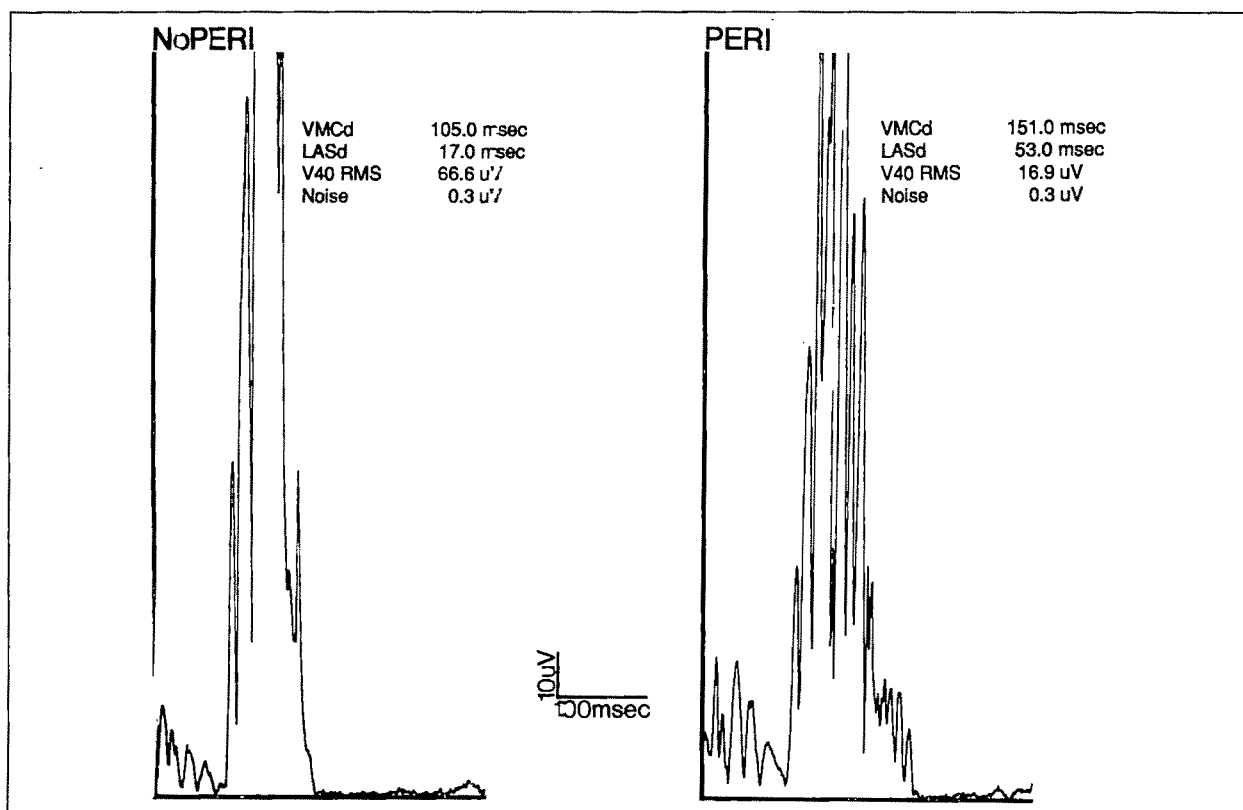


FIGURE 4. Signal-averaged vector magnitude complex (VMC) of the patient without peri-infarction block (NoPERI) and the patient with peri-infarction block (PERI) whose standard electrocardiograms appear in Figures 1 and 2. Note in the PERI patient the increased total duration of the VMC (VMCd), the prolongation of the terminal potential $<40 \mu$ V (LASd) and the very low amplitude and fragmented morphology of the last 40 ms (V40 RMS). In contrast, in the NoPERI patient, there is a morphologically sharp descent of the terminal voltage, VMCd, and a relatively high amplitude of the last 40 ms of the VMC.

DISCUSSION

In 1952 Langner et al⁴² reported the relation between the presence of coronary artery disease and the appearance of notches (change in slope and sign of the fundamental QRS) and slurs (change in slope without change of sign of the fundamental QRS). In a prospective postmortem study of 128 human hearts, using high-speed, high fidelity techniques, our group reported a significant difference in quantitative notch occurrence between patients with anatomic evidence of MI and normal subjects.⁴³ In a later, similar study of 130 hearts, we were able to correlate the site of infarction with the site of maximal notching in the X or Y lead.⁴⁴ The greatest value of the notch recognition was, perhaps, the effectiveness in localizing MI in certain patients without diagnostic Q waves.⁴⁵ These hearts had a significant amount of stippled intramural MI, sometimes without recognizable epicardial or endocardial breakthrough of fibrous scar. Fenoglio,⁴⁶ Gardner⁴⁷ and their co-workers offered strong evidence that fragmented electrocardiograms are likely to be found wherever myocardial fibers were separated by fibrous connective tissue; the correspondence between fragmented electrocardiograms directly recorded from the heart and ventricular late potentials from the body surface was reported by Simson et al.³¹ These observations, and the fact that the peri-infarction block pattern in inferior wall MI shares some features of timing of late potentials as well as morphology of notches and slurs, were the bases for the present inquiry.

It appears that electrocardiograms from patients with Q-wave inferior wall MI can be separated into 2 categories. In the first, the electrocardiogram reflects very definite diagnostic Q waves, but once the wave of activation has proceeded beyond 30 to 40 ms, the remainder of the QRS complex is smooth, rapid and suggests no further interruption or slowing of the activation process. In the other group, the group with the peri-infarction block pattern, diagnostic Q waves are also prominent, but there appears to be a distinct interruption of the rapid, smooth completion of the excitation process. It is in this group that ventricular late potentials have been found in the present study to be exceptionally abundant. We believe that it is likely that the underlying anatomic derangement and the resulting pathophysiology of the myocardium after MI (which provides the substrate producing the late QRS abnormality referred to as peri-infarction block) is very likely the same substrate resulting in the low-level abnormal terminal potential referred to as ventricular late potentials. The recognition of ventricular late potentials has been helpful in identifying the post-MI patient at an increased risk for sustained ventricular arrhythmias.^{29-37,46} The higher incidence of late potentials in the peri-infarction group, along with the higher incidence of sustained ventricular arrhythmias in the peri-infarction group than in the group without peri-infarction block, suggests that patients in whom peri-infarction block accompanies inferior wall MI may be at higher risk for sustained ventricular arrhythmias than are individuals with inferior wall MI who have no ter-

минаl abnormality of QRS. Although the number examined here is reasonably large, an even larger study would be valuable for further confirmation.

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Comparison of Right Ventricular Impedance, Pulse Pressure and Maximal dP/dt for Determination of Hemodynamic Stability of Ventricular Arrhythmias Associated with Coronary Artery Disease

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By monitoring hemodynamic parameters, a future generation of automatic implantable defibrillators will provide tiered therapy of ventricular arrhythmias according to the associated hemodynamic compromise. Changes in intracardiac impedance permit beat-to-beat assessment of ventricular volumes and make this parameter attractive as a rapid discriminator of hemodynamic compromise during arrhythmias. Beat-to-beat changes in right ventricular (RV) impedance were measured before, during and after 27 episodes of ventricular tachyarrhythmias induced in 17 men (64 ± 7 years, mean \pm standard deviation; left ventricular ejection fraction $41 \pm 11\%$). Impedance was measured using a tri-polar lead system and was compared to ventricular tachycardia cycle length, RV pulse pressure and maximum systolic RV dP/dt as indicators of systemic hemodynamic compromise. The average decreases in systolic blood pressure and mean arterial pressure during ventricular tachycardia were $48 \pm 23\%$ and $46 \pm 26\%$, respectively (mean \pm standard deviation; $p < 0.001$ for each). Right ventricular impedance decreased an average $39 \pm 22\%$ from its baseline value ($p < 0.001$) during ventricular tachycardia. The percent change in impedance from baseline during ventricular tachycardia correlated significantly with the percent decrease in systolic and mean arterial pressure ($r = 0.45$ and 0.42 , respectively; both $p < 0.05$). Right ventricular dP/dt correlated the most poorly of all parameters with changes in blood pressure while impedance \times RV pulse pressure correlated best with changes in mean and systolic pressure ($r \geq 0.82$, $p < 0.001$). (Am J Cardiol 1990;66:575-582)

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The present generation of automatic implantable cardioverter/defibrillators detects and responds to cardiac arrhythmias based solely on measurement of tachycardia cycle length or fulfillment of probability density function criteria. An implantable device that can deliver tiered therapy directed by a hemodynamic sensor would be useful in the management of patients with multiple morphologies of tachycardia producing different symptoms. It is necessary, therefore, to identify hemodynamic parameters that are closely correlated with the changes in blood pressure and predictive of the severity of symptoms that accompany an arrhythmia. Such a parameter must also be feasible for monitoring by implanted devices.

Cardiac impedance as measured with the multipolar catheter technique has been shown to correlate with changes in stroke volume and cardiac output in canines and in humans.¹⁻³ Because the impedance technique can provide beat-to-beat estimation of these cardiac parameters, it may be able to rapidly differentiate hemodynamically stable from unstable tachycardias. Right ventricular (RV) pulse pressure and maximal RV dP/dt may also be useful variables for discriminating hemodynamically stable from unstable ventricular tachyarrhythmias.

In this study, we compared ventricular tachycardia cycle length and changes in RV impedance, RV pulse pressure and maximal positive RV dP/dt during ventricular tachycardia with concomitant changes in arterial pressure to determine which variable(s) most closely correlated with changes in systemic hemodynamics during episodes of tachycardia.

METHODS

Study patients: We studied 28 consecutive subjects with documented or suspected ventricular tachyarrhythmias referred to the Hunter Holmes McGuire Veterans Affairs Medical Center for clinical electrophysiology studies. All patients gave written informed consent to a protocol approved by the Committee on the Conduct of Human Research at the Medical College of Virginia, the McGuire Veterans Administration Medical Center and the Clinical Research Board at Teletronics Corporation. The study group comprised 17 men with a total of 27 episodes of ventricular tachyarrhythmias that

yielded technically suitable data for analysis. The patients ranged in age from 45 to 76 years (64 ± 7 years, mean \pm standard deviation). All 17 patients had significant atherosclerotic coronary artery disease. Two patients had concomitant aortic or mitral valvular disease, or both. Twelve patients had previous myocardial infarctions. The average left ventricular ejection fraction was $41 \pm 11\%$ and ranged from 22 to 60%. Twelve episodes of ventricular tachycardia occurred in the absence of anti-arrhythmic drug therapy, while the remainder occurred with amiodarone (7), procainamide (4), amio-

darone and procainamide (1), diprafenone (2) or quinidine (1).

Electrophysiology studies: All studies were performed using quadripolar catheters (Bard Corp.) positioned under fluoroscopy in the right atrium and right ventricle through the femoral vein. Systemic blood pressure was recorded continuously through a 5Fr or 6Fr femoral artery sheath. Programmed electrical stimulation was performed using a custom-designed stimulator (Bloom Associates) delivering pacing pulses at twice diastolic threshold. Surface and intracardiac electrocar-

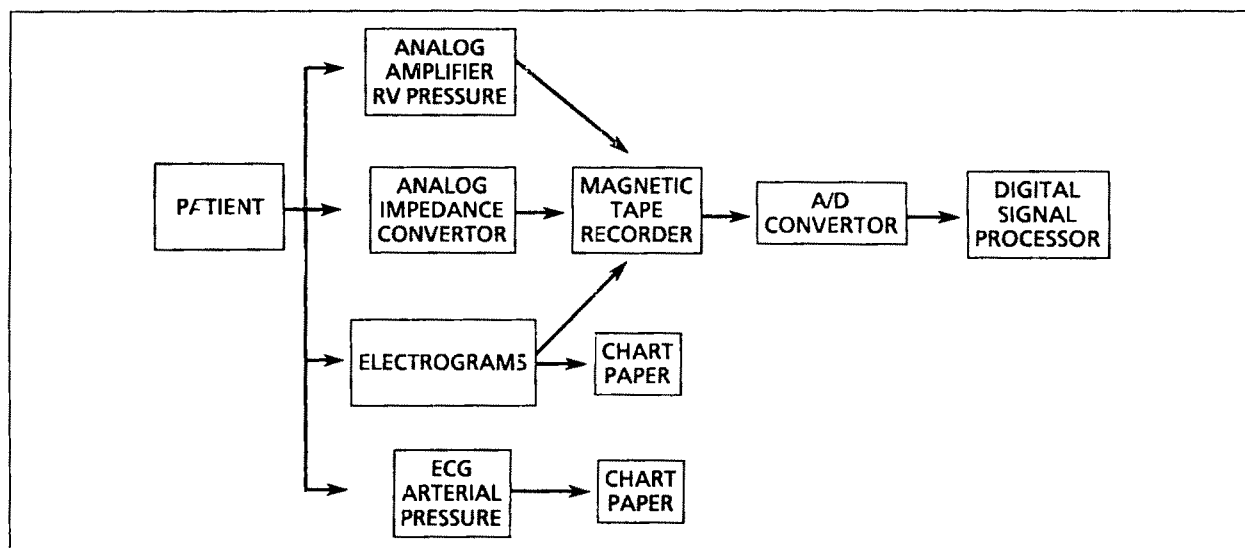


FIGURE 1. Schematic showing data acquisition and recording. Analog recordings of right ventricular pressure tracings, impedance signals and bipolar atrial and ventricular electrograms were made on a multichannel magnetic tape recorder. After digitization at 200 Hz, data analysis was performed on a personal computer programmed for digital signal analysis. A/D = analog/digital; ECG = electrocardiogram.

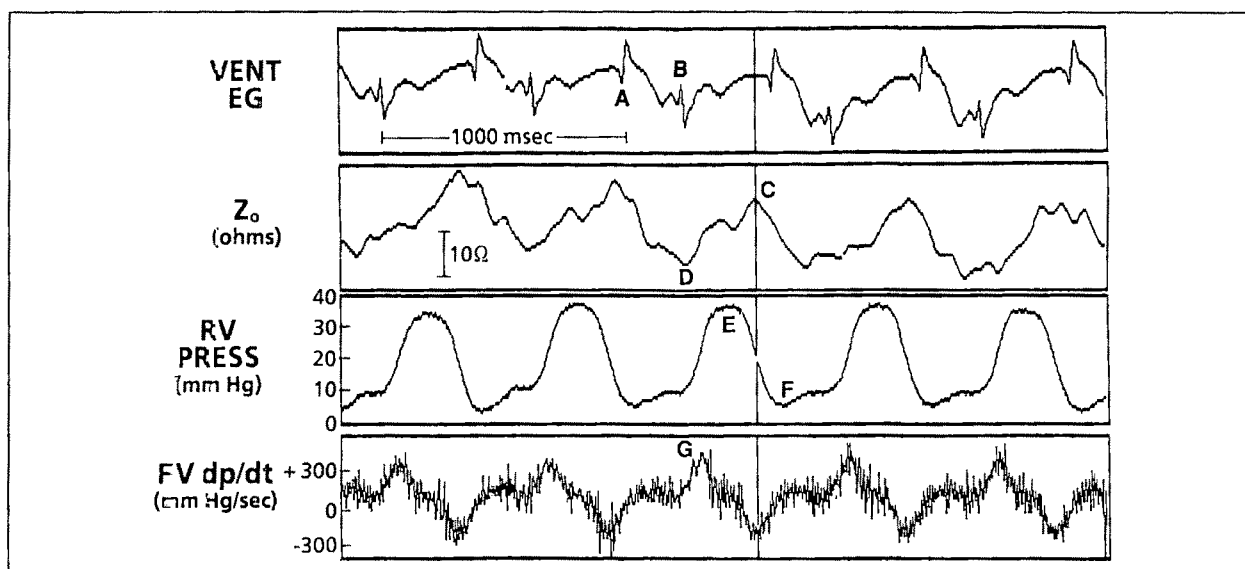


FIGURE 2. Four-channel display of data analysis program on personal computer. Data acquired during sinus rhythm. A and B are the atrial and ventricular electrocardiograms, respectively. The sinus cycle length is 610 ms. C is the maximal right ventricular impedance and D the minimal impedance for the cardiac cycle begun at A; the change in impedance (Z) from C to D is 18 ohms. Right ventricular pulse pressure is the difference between points E and F, i.e., 29 mm Hg. Maximal systolic right ventricular dp/dt is defined by point G (335 mm Hg/s). The vertical line is the movable electronic cursor. RV dp/dt = first derivative of the RV pressure waveform; RV PRESS = right ventricular pressure; VENT EG = ventricular electrogram; Z_0 = impedance.

diagrams were displayed and recorded using a physiologic recorder (Electronics for Medicine VR-16) at standard gain settings. Programmed electrical stimulation was performed according to a previously published protocol.⁴

Impedance: Right ventricular impedance was measured using a tripolar lead system. This system comprised the first and third poles of a standard 6Fr quadripolar catheter (1 cm spacing) positioned in the right ventricular apex and a large surface patch electrode (R2 Co.) adherent to the anterior left shoulder. The right ventricular catheter was positioned in the distal apex under fluoroscopy. A symmetric biphasic current pulse with a peak-to-peak amplitude of 200 μ A, duration of 10 μ s and frequency of 90 Hz was produced from a custom-designed pulse generator (Teletronics Pacing Corp.) and delivered into the right ventricular cavity through the distal-most ring electrode of the quadripolar catheter. This current represents approximately 0.2% of a standard pacing pulse and has been used safely in previous studies.⁵ The electrical potential resulting from each current pulse was measured between the surface patch (electrically grounded) and the proximal electrode of the right ventricular catheter. The impedance to current flow (Z_0) was calculated for each pulse by an on-line computer using Ohm's law, $Z_0 = V/I$, with current (I) known to be 200 μ A, voltage (V) measured and impedance expressed in ohms. The phasic time-varying impedance signal was filtered at 20 Hz before being recorded on a multichannel FM cassette recorder (Teac HR-30G).

Right ventricular pulse pressure: Right ventricular pressure was measured continuously using a 5Fr micromanometer-tipped catheter (Millar Instruments) introduced through the femoral vein and positioned in the right ventricular apex under fluoroscopy. The catheter

TABLE I Hemodynamic Parameters During Ventricular Tachycardia

	CL (ms)	ΔZ (ohms)	$\Delta RVPP$ (mm Hg)	$\Delta dp/dt$ (mm Hg/s)	$\Delta Z \cdot RVPP$ (ohm \cdot mm Hg)
ΔSBP (mm Hg)	$r = 0.53$ $p = 0.008$	0.40 0.05	0.29 0.20	0.46 0.04	0.25 0.26
ΔMAP (mm Hg)	$r = 0.57$ $p = 0.004$	0.24 0.25	0.39 0.08	0.39 0.09	0.27 0.23
% ΔSBP	$r = 0.57$ $p = 0.004$	0.45 0.028	0.79 0.0001	0.41 0.07	0.86 0.0001
% ΔMAP	$r = 0.57$ $p = 0.004$	0.42 0.04	0.76 0.0001	0.34 0.14	0.82 0.0001

Pearson correlation coefficients and p values for the relations between absolute and relative changes in measured hemodynamic parameters and absolute and relative changes in systemic SBP and MAP.

CL = cycle length; MAP = mean arterial pressure; RVPP = right ventricular pulse pressure; SBP = systolic blood pressure; Z = change in impedance; Z \cdot RVPP represents the arithmetic product of change in impedance and right ventricular pulse pressure; Δ = absolute change from baseline values; % Δ = percent change from baseline values.

and accompanying bridge amplifier possess 5 μ V/V/mm Hg sensitivity and a normal frequency of 20 KHz. The Millar catheter-amplifier system was calibrated immediately before insertion and the calibration was verified at the end of each study. The continuous right ventricular pressure tracing was also recorded on the multichannel FM cassette recorder.

Data acquisition and analysis: Intracardiac bipolar electrocardiograms (atrial and ventricular), right ventricular pulse pressure and impedance signals were recorded simultaneously on the multichannel cassette recorder. The data were annotated on-line with a personal computer (Hewlett Packard 110) via an RS-232 port. The data from the cassette tape were digitized at 200 Hz using a 12 bit analog/digital converter (Digital Equipment Corp.) and stored on magnetic disks. A custom-designed computer program was used to display

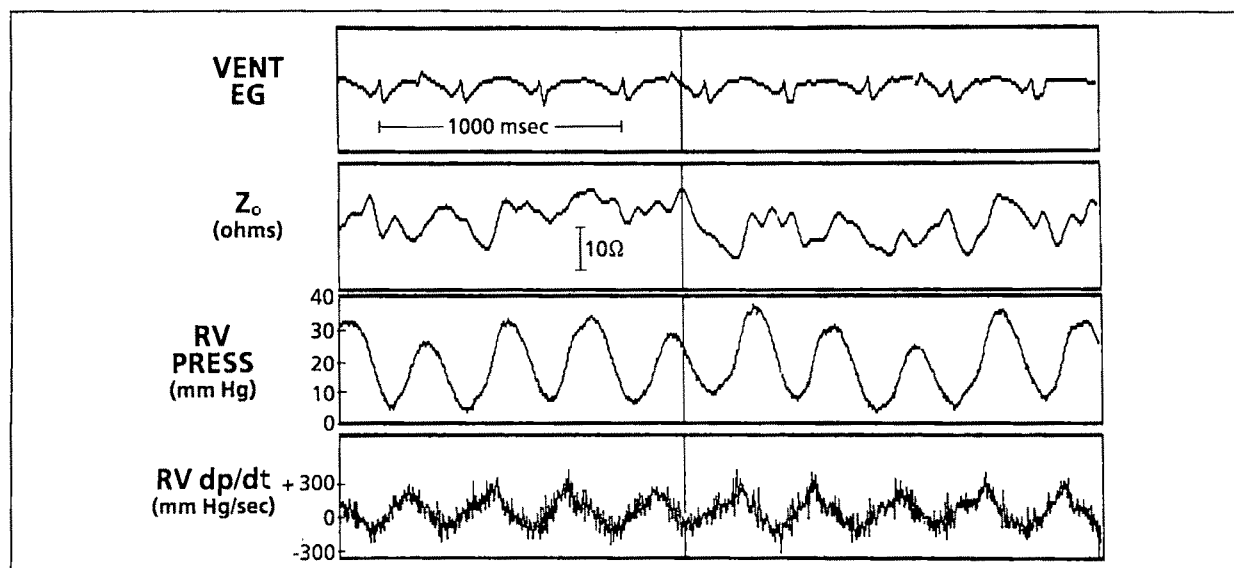


FIGURE 3. Four-channel display of data acquired during ventricular tachycardia from the same patient in Figure 2. Cycle length = 330 ms; change in impedance = 8 ohms; right ventricular pulse pressure = 13 mm Hg; maximum systolic dp/dt = 217 mm Hg/s for the cardiac cycle containing the electronic cursor. Systolic blood pressure and mean arterial pressure decreased 62 and 56%, respectively, during this episode. Abbreviations as in Figure 2.

and analyze up to 4 data signals simultaneously on a Compaq Portable II computer (Figure 1). This program allowed display of the signals at different time sweeps, determination of signal amplitude at any point, measurement of the time interval between any 2 signal points (at 5-ms increments) and calculation and display of the derivative of any signal (Figure 2).

Impedance, RV pressure and ventricular cycle length were measured in a beat-to-beat fashion for 10 consecutive beats before initiation of programmed electrical stimulation (baseline), for the first 20 beats of induced or spontaneous ventricular tachyarrhythmias and for the first 10 beats after the termination of the tachyarrhythmias (recovery). Maximum systolic RV dP/dt was estimated during baseline, during recovery and during the first 10 beats of ventricular tachycardia.

The impedance signal was analyzed for relative change in amplitude during each cardiac cycle. Because of the occurrence of baseline artifact or multiple peaks, especially during ventricular arrhythmias, the peak impedance value was taken to be the maximal impedance amplitude occurring between the peak RV systolic pressure and the nadir of RV diastolic pressure for the same beat (Figures 2 and 3). The minimum impedance value for a given cardiac cycle was taken to be the nadir of the impedance signal occurring between the peak value for the same cardiac cycle and the peak value of the preceding cardiac cycle. The change in impedance was calculated for each cardiac cycle by subtracting the minimum from the maximum values. When the RV pressure tracing was not available (5 episodes), the absolute peak and trough values for impedance in each cardiac cycle were used to determine the change in impedance.

Right ventricular pulse pressure was determined for each beat analyzed for change in impedance. Right ventricular pulse pressure was defined as the difference between the maximal and subsequent minimal values for RV pressure during a given cardiac cycle. Maximum systolic RV dP/dt was determined from the computer-derived first derivative of the RV pressure signal and

cycle length was measured as the interval between peak deflections of the QRS complexes.

Statistics: The beat-to-beat values for change in impedance, RV pulse pressure, dP/dt and cycle length measured during baseline, ventricular tachycardia and recovery were arithmetically meaned for each episode of tachycardia. A paired *t* test was used to determine the significance of changes in each hemodynamic variable from baseline to ventricular tachycardia and recovery. A Wilcoxon rank sum test was used to compare the systemic hemodynamic changes between 2 groups of patients. Pearson correlation coefficients were derived from simple linear regression. The level of statistical significance was $p < 0.05$. All values are expressed as mean \pm standard deviation.

RESULTS

Ventricular arrhythmias: Twenty-seven episodes of ventricular tachyarrhythmias were induced in 17 patients. The rhythm was sustained monomorphic ventricular tachycardia (>30 seconds duration) in 23 episodes, non-sustained monomorphic ventricular tachycardia in 2 episodes and ventricular fibrillation (cycle length = 160 to 180 ms) in 2 episodes. The average cycle length for all episodes was 313 ± 100 ms.

Systemic hemodynamic changes: Systolic blood pressure decreased during each episode of ventricular tachyarrhythmia. Mean arterial pressure decreased with each episode of ventricular tachycardia except 1. The mean baseline systolic blood pressure was 135 ± 17 mm Hg and the average baseline mean arterial pressure was 93 ± 8 mm Hg. The average decreases in systolic blood pressure and mean arterial pressure during ventricular tachycardia were 66 ± 33 mm Hg and 42 ± 24 mm Hg, respectively (both $p < 0.001$). The average percent changes in systolic blood pressure and mean arterial pressure from baseline were -48 ± 23 and $-46 \pm 26\%$, respectively.

Impedance: The average baseline value for change in impedance before induction of ventricular tachycardia was 21 ± 8 ohms. During ventricular tachycardia,

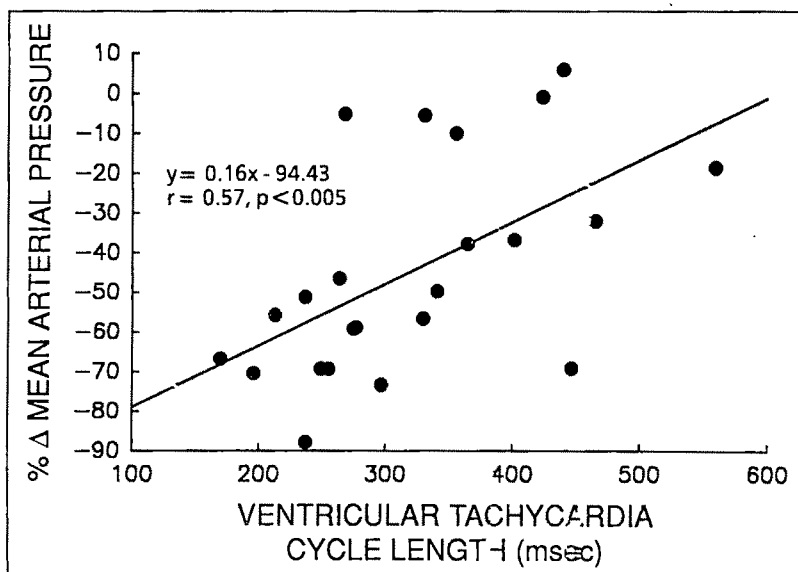


FIGURE 4. Graph of ventricular tachycardia cycle length versus percent changes in mean arterial pressure.

the change in impedance decreased significantly to 12 ± 6 ohms ($p < 0.001$). In recovery, the change in impedance averaged 20 ± 8 ohms, significantly greater than the change in impedance in ventricular tachycardia ($p < 0.001$), but similar to the baseline values ($p > 0.50$). The change in impedance was not significantly different for beats 1 to 10 of ventricular tachycardia compared to beats 10 to 20 or beats 1 to 20. During ventricular tachycardia, the average percent decreases in change in impedance from baseline and recovery were 39 ± 22 and $36 \pm 18\%$, respectively.

Right ventricular pulse pressure: The average baseline right ventricular pulse pressure was 40 ± 29 mm Hg and this value did not change significantly during recovery (41 ± 26 mm Hg). During ventricular tachyarrhythmia, right ventricular pulse pressure averaged 16 ± 15 mm Hg, significantly lower than during baseline or recovery (both $p < 0.001$). The average percent decrease in right ventricular pulse pressure from baseline was $57 \pm 26\%$. Maximal right ventricular dP/dt

during ventricular tachyarrhythmia was 355 ± 325 mm Hg/s. This value was significantly less than baseline, 515 ± 298 mm Hg/s ($p = 0.01$), and recovery, 690 ± 331 mm Hg/s ($p < 0.001$).

Impedance \times right ventricular pulse pressure: Impedance \times RV pulse pressure is the arithmetic product of the values for change in impedance and for right ventricular pulse pressure. The value of impedance \times RV pulse pressure was found to be 853 ± 900 ohm \times mm Hg during baseline and 244 ± 393 ohm \times mm Hg during ventricular tachyarrhythmias ($p < 0.001$). In recovery, impedance \times RV pulse pressure averaged $954 \pm 1,085$ ohm \times mm Hg, also significantly greater than the value in ventricular tachycardia ($p < 0.001$). In ventricular tachycardia, impedance \times RV pulse pressure decreased an average of $73 \pm 24\%$ from baseline ($p < 0.001$).

Correlations with systemic hemodynamics: The correlation coefficients for ventricular tachycardia cycle length, RV pulse pressure, RV dP/dt and impedance \times

FIGURE 5. Graph of percent change right ventricular impedance (Z) versus percent change systolic blood pressure.

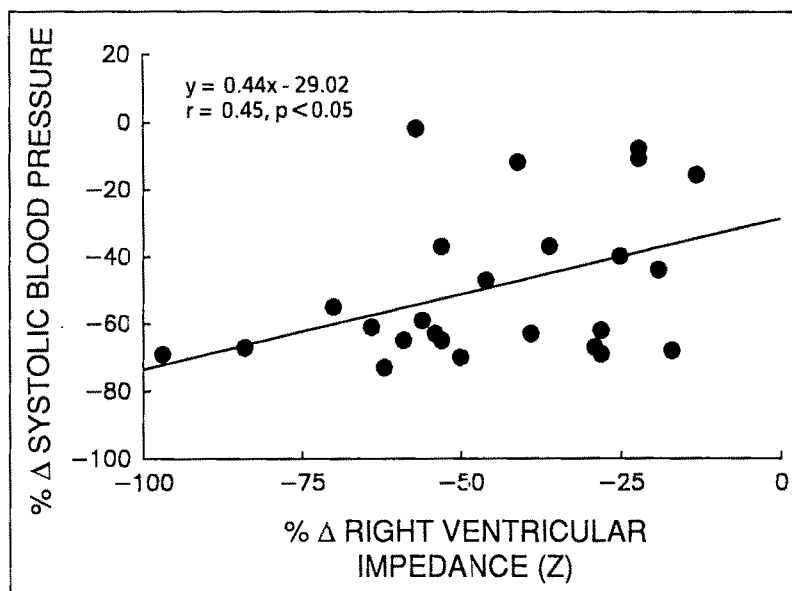
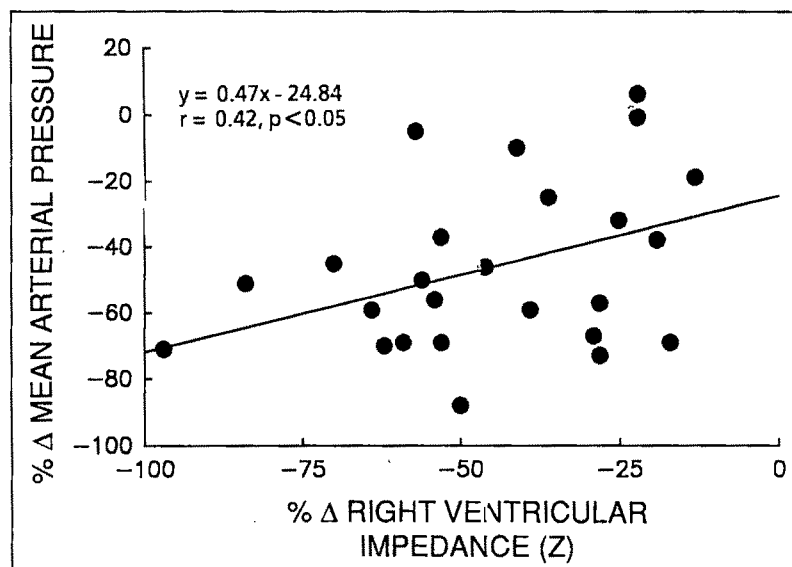


FIGURE 6. Graph of percent change right ventricular impedance (Z) versus percent change in mean arterial pressure.



RV pulse pressure with absolute and percent changes in systemic arterial pressures are listed in Table I.

Ventricular tachycardia cycle length correlated significantly with absolute and percent changes in mean arterial pressure and systolic blood pressure (all $r = 0.53$ to 0.57 , all $p < 0.01$). The relation between percent change in mean arterial pressure and ventricular tachycardia cycle length is shown in Figure 4. Changes in impedance correlated poorly with absolute changes in both mean arterial pressure and systolic blood pressure. The percent change in mean arterial pressure and percent change in systolic blood pressure were less closely correlated with percent change in impedance than with ventricular tachycardia cycle length, but still achieved statistical significance (Figures 5 and 6). Change in right ventricular pulse pressure correlated poorly with the absolute change in blood pressure (both $r \leq 0.37$, both $p > 0.08$). There was, however, a close relation be-

tween percent change in right ventricular pulse pressure and percent changes in mean arterial pressure and systolic blood pressures (Figures 7 and 8). The percent changes in dP/dt showed no significant relation to percent changes in blood pressure ($p \geq 0.07$). The closest correlation was obtained from the relations between percent changes in impedance \times RV pulse pressure and percent changes in mean arterial and systolic blood pressures; $r = 0.82$ and 0.86 respectively, both $p < 0.001$ (Figures 9 and 10).

DISCUSSION

Future generations of automatic implantable cardioversion defibrillator devices will likely incorporate hemodynamic sensors to direct tiered therapy of ventricular arrhythmias based on the degree of hemodynamic compromise accompanying the tachycardia. These tiered responses may include pacing algorithms for he-

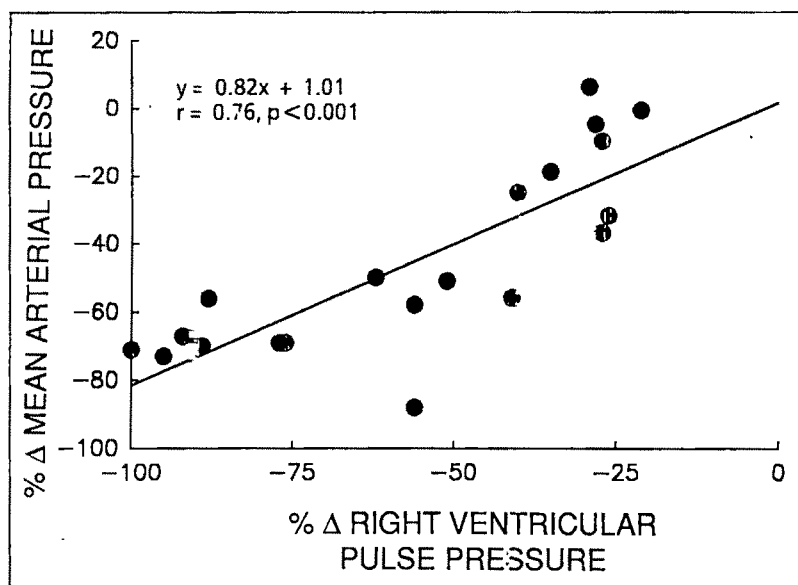


FIGURE 7. Graph of percent change right ventricular pulse pressure versus percent change in mean arterial pressure.

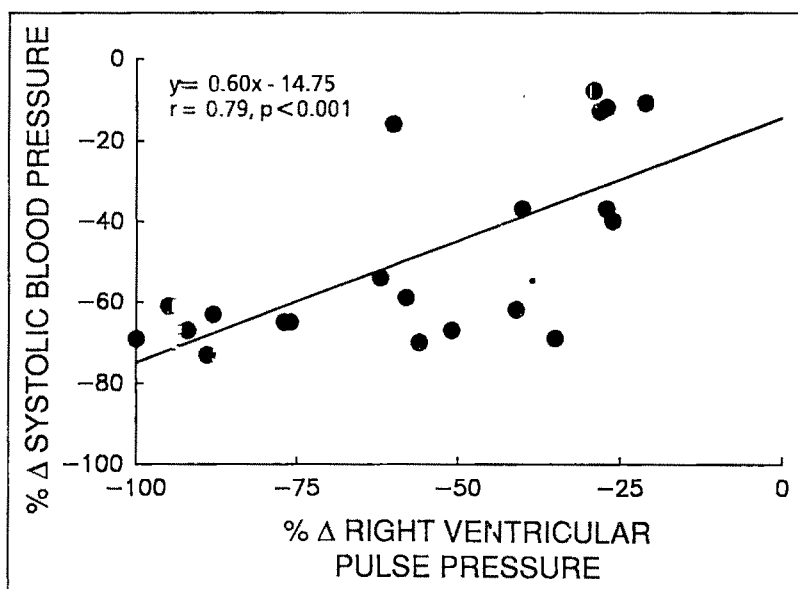


FIGURE 8. Graph of percent change right ventricular pulse pressure versus percent change in systolic blood pressure.

modynamically stable rhythms, and immediate cardioversion for unstable ones.

The theory of the measurement of cardiac impedance has been reviewed in detail elsewhere.^{2,6} Briefly, intracardiac impedance measurements reflect cyclic changes in cardiac blood volume that alter the electrical resistance (impedance) between 2 or more intracardiac electrodes. Measured intracardiac volume is proportional to the distance between sensing electrodes squared and inversely proportional to the electrical impedance of the primary conductor (blood) between the electrodes.² Highly accurate estimates of absolute left ventricular volumes may be obtained by the impedance technique.¹⁻³ Similarly, the impedance technique accurately reflects volumetric changes in the right ventricle;^{3,7,8} however, the complex right ventricular anatomy results in significant underestimation of absolute right ventricular volumes.⁷

We studied the relation between changes in right ventricular impedance, an indicator of relative changes

in right ventricular volume, and the hemodynamic changes occurring with induced ventricular tachyarrhythmias. Changes in impedance were compared to ventricular tachycardia cycle length, right ventricular pulse pressure, impedance \times RV pulse pressure and maximal right ventricular dP/dt as predictors of hemodynamic compromise. The percent changes in impedance correlated significantly ($p < 0.05$), but not closely ($r \leq 0.45$) with percent changes in mean arterial and systolic blood pressure. The percent change in right ventricular pulse pressure correlated well with relative systemic hemodynamic changes ($r \geq 0.76$) while ventricular tachycardia cycle length was intermediate between the change in impedance and right ventricular pulse pressure in relation to changes in systemic blood pressures. Percent change in right ventricular dP/dt correlated the most poorly with the percent changes in arterial pressures during arrhythmias ($r \leq 0.41$, $p \geq 0.07$).

The reasons for the relatively poor correlation between changes in impedance and systemic hemodynam-

FIGURE 9. Graph of the arithmetic product of change in impedance (Z) and right ventricular pulse pressure (RVPP), percent change $Z \times RVPP$, versus percent change in mean arterial pressure.

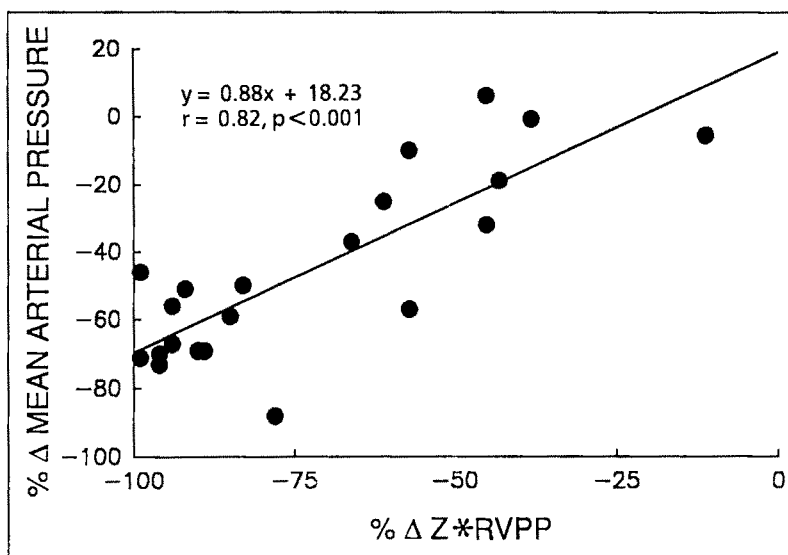
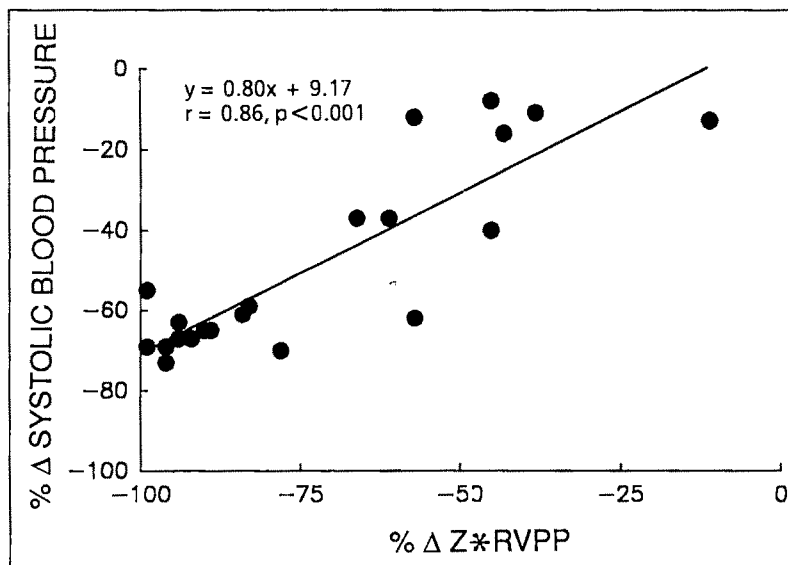


FIGURE 10. Graph of percent change $Z \times RVPP$ versus percent change in systolic blood pressure. Abbreviations as in Figure 9.



ic changes are speculative. Obviously, effective left ventricular cardiac output is dependent on adequate diastolic filling provided by right ventricular output. It is the left ventricle, however, which generates systemic blood pressure. Thus, there may be a disproportionate impairment of right ventricular and left ventricular function at rest or during ventricular tachyarrhythmias, or both.

Even with multipolar impedance catheter systems, some right ventricular segments are not represented in the determination of impedance due to incomplete transversion of the right ventricle by the catheter.⁷ It is possible that the right ventricular segments assessed by the catheter are not representative of overall right ventricular function. Flood flow itself may alter the resistivity of blood and thereby alter impedance independent of volumetric changes.⁹ The baseline artifact during the recording of impedance may also have obscured the true magnitude of impedance change in some episodes. In addition, the influences of baseline right ventricular function, the presence of tricuspid or pulmonic regurgitation, effects of extracardiac blood flow, current flow through myocardial and extracardiac tissues and alterations in right ventricular geometry may all contribute to inaccuracies in the relation between impedance and volume.

The highest correlation with systemic hemodynamic changes was provided by percent change in impedance \times RV pulse pressure. The correlations are striking (Figures 9 and 1C). Without knowledge of the true relation of impedance to total ventricular volume, the cardiovascular parameter(s) defined by the value of impedance \times RV pulse pressure is uncertain. However, if impedance is indicative of relative right ventricular volume changes, the value impedance \times RV pulse pressure may be related to right ventricular stroke work output.

Other investigators have measured right ventricular impedance during ventricular tachyarrhythmias. Khoury et al¹⁰ found RV impedance to decline minimally during hemodynamically stable ventricular and supraventricular tachyarrhythmias. Unstable ventricular tachyarrhythmias resulted in much greater reductions in impedance. There was a significant correlation between the changes in RV impedance and the percent mean arterial pressure associated with these tachyarrhythmias.

Study limitations: Perhaps the greatest limitation inherent to this study is the use of the tripolar lead system for recording right ventricular impedance. This system differs from these lead configurations that are completely contained in the ventricle. The extracardiac position of 1 sensing electrode (shoulder patch) introduces several vascular and perfused anatomic structures into the electrical "circuit." Thus, alterations in perfusion of these organs and the flow of blood itself may influence the measurement of impedance in a manner characteristic to this lead configuration. Since even multipolar

impedance catheter systems fail to account for all right ventricular segmental changes, the use of a single intraventricular sensing lead may accentuate this limitation. In addition, the distance between sensing electrodes is not truly fixed and may also influence the impedance determination. The respiratory component of the impedance signal was not actively filtered because of the known influence of respiration on RV volume. All studies were performed in the supine position and the effect of upright posture and changes in autonomic tone on the measurement of hemodynamics may be underestimated by this study.

Only 17 of 28 (61%) of patients studied had technically adequate electrocardiograms, RV pressure and impedance waveforms for analysis. Most problematic was the frequent occurrence of baseline artifact during the recording of impedance. The source(s) of interference is not known, but probably relates to electronic noise, catheter motion artifact, muscle contraction artifact or poor electrical interface between the patient and the surface lead. The use of a higher frequency current with greater amperage would theoretically reduce electrical noise in this system.

Despite its limitations, this method of impedance determination was used due to its relative electronic simplicity and resemblance to a system shown reliable for monitoring ventilatory parameters in a permanent pacemaker.¹¹

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Risk Stratification of Left Ventricular Hypertrophy in Systemic Hypertension Using Noninvasive Ambulatory Blood Pressure Monitoring

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Twenty-four-hour noninvasive ambulatory blood pressure (BP) monitoring and echocardiography were performed in 165 consecutive untreated hypertensive patients and in 92 healthy subjects. In the hypertensive group, left ventricular (LV) mass index showed closer correlations (all $p < 0.01$ in the comparisons between the r coefficients) with average 24-hour ambulatory systolic ($r = 0.47$) and diastolic ($r = 0.33$) BP than with casual systolic ($r = 0.35$) and diastolic ($r = 0.28$) BP. Hypertensive patients were classified according to the difference between their observed and predicted levels of ambulatory BP (the latter assessed by regressing the observed ambulatory BP on the casual BP). When compared to those with lower than predicted ambulatory BP (≤ 10 mm Hg systolic, ≤ 6 mm Hg diastolic), patients with higher than predicted ambulatory BP (≥ 10 mm Hg systolic and ≥ 6 mm Hg diastolic) had higher values of LV mass index and other indexes of LV hypertrophy (all $p < 0.01$) but had similar values of casual BP. Prevalence of LV hypertrophy was 6 to 10% in the former and 35 to 39% in the latter ($p < 0.001$). None of the indexes of LV structure differed between the group with low ambulatory BP and the normotensive group. It is concluded that hypertensive patients whose ambulatory BP readings are notably higher than one would predict from clinical BP readings are at highest risk of LV hypertrophy, an independent prognostic marker. Noninvasive ambulatory BP monitoring identifies a subset of hypertensive patients in whom the routine echocardiographic examination of the left ventricle is recommended.

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Casual blood pressure (BP)^{1,2} and electrocardiographic left ventricular (LV) hypertrophy^{3,4} are well known independent predictors of cardiovascular morbidity and mortality. Recent evidence suggests that noninvasive ambulatory BP readings may be superior to casual BP readings in predicting future cardiovascular events.^{5,6} In fact, when comparing hypertensive patients with observed ambulatory BP above versus below a definite limit with respect to their predicted ambulatory BP levels (obtained by regressing ambulatory BP values on casual BP values), those with BP above a definite limit had a greater long-term incidence of fatal and nonfatal events.^{5,6} These results have been substantially confirmed using intraarterial BP monitoring.⁷ Because ambulatory rather than casual BP is more closely related to LV mass,⁸⁻¹¹ one reason for the ability of ambulatory BP readings to discriminate between high- and low-risk subjects may be the identification of subsets of patients with different degrees of echocardiographic LV hypertrophy, an independent risk marker,¹²⁻¹⁵ who would be in the same risk group if only casual BP and electrocardiography were used. To clarify the relations between casual BP, ambulatory BP and LV structure in the light of such epidemiologic findings, we studied a large group of hypertensive patients and control subjects using noninvasive ambulatory BP monitoring and echocardiography.

METHODS

Patients: We studied 165 patients with essential hypertension (47% women) and 92 healthy normotensive subjects (50% women). They were consecutively chosen among patients with essential hypertension and healthy normotensive subjects examined in our laboratory from 1986 to 1989, partly included in a previous study on the effects of nocturnal BP reduction on LV mass,¹¹ and meeting all the following criteria: (1) no antihypertensive drugs for ≥ 4 weeks; (2) good quality echocardiographic tracings; (3) agreement within 5 mm Hg between BP recording unit and mercury sphygmomanometer in ≥ 3 consecutive measurements obtained simultaneously on the same arm before beginning ambulatory BP recording; and (4) absence of clinical, electrocardiographic or echocardiographic evidence of coronary or valvular disease, renal disease, transient cerebral ischemic attacks or stroke. In the hypertensive group, supine diastolic BP had to be ≥ 90 mm Hg in ≥ 3 visits at

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TABLE I Main Findings in the Study Population

Variables	Normotensive Subjects (n = 92)	Hypertensive Patients (n = 165)	Analysis of Variance	
			F	p
Age (years)	50 (14)	52 (12)	1.8	0.2
Height (cm)	168 (8)	166 (9)	0.2	0.6
Weight (kg)	73 (12)	75 (14)	0.8	0.4
BSA (m ²)	1.80 (0.2)	1.83 (0.2)	1.0	0.3
Casual BP (mm Hg)				
Systolic	136 (13)	159 (18)	119.1	<0.0001
Diastolic	80 (7)	98 (7)	411.2	<0.0001
Average 24-hour BP (mm Hg)				
Systolic	123 (13)	142 (16)	84.1	<0.0001
Diastolic	79 (8)	92 (8)	144.9	<0.0001
Heart rate (beats/min)				
Casual	73 (10)	76 (12)	5.8	0.016
Average 24-hour	73 (6)	76 (8)	11.4	0.0008
End-diastolic IVS thickness (cm)	0.79 (0.2)	0.96 (0.3)	22.8	<0.0001
End-diastolic PW thickness (cm)	0.71 (0.1)	0.82 (0.2)	25.8	<0.0001
LV end-diastolic diameter (cm)	5.29 (0.6)	5.28 (0.7)	0.001	0.75
Shortening fraction (%)	40 (7)	38 (7)	3.5	0.061
LV mass (g)	139 (46)	175 (69)	20.4	<0.0001
LV mass index (g/m ²)	77 (23)	95 (34)	21.5	<0.0001
Relative wall thickness	0.27 (0.07)	0.31 (0.08)	18.4	<0.0001
Cross-sectional area (cm ²)	14.2 (3.6)	17.4 (5.3)	25.3	<0.0001
Cross-sectional area index (cm ² /m ²)	7.9 (1.9)	9.5 (2.6)	25.3	<0.0001

Data expressed as mean ± standard deviation.
BP = blood pressure; BSA = body surface area; IVS = interventricular septum; LV = left ventricular; PW = posterior wall.

1-week intervals, and all the 4 aforementioned criteria had to be fulfilled. Altogether, 114 hypertensive patients (69%) had never received antihypertensive drugs. Most normotensive subjects were healthy people referred to our center for a clinical checkup including echocardiography and ambulatory BP monitoring, and showing casual BP constantly <160/90 mm Hg.

Experimental procedure: BLOOD PRESSURE MEASUREMENTS: Clinical BP was measured after 10 minutes of supine rest by using a Hawksley Random Zero manometer (phase I and V) (Hawksley and Sons, Ltd, Lancing, West Sussex, England), with deflation rate fixed at 2 mm Hg/beat. Ambulatory BP was recorded by using the fully automatic units ICR 5200 and 90202 (Spacelabs, Redmond, Washington). In our laboratory, the ICR 5200 unit showed a correlation of 0.97 with both systolic and diastolic pressures measured simultaneously

on the same arm using a mercury sphygmomanometer.¹⁶ Other investigators have reported a similar correlation with the same unit.¹⁷ Bladders of appropriate size (13 cm × 24 cm, 17 cm × 32 cm) were used. Mean arm circumference was 26.3 cm (standard deviation [SD] 3). The reading and analysis of data provided by the unit was done using the ABP5600 and ABP90204 interfaces (Spacelabs), with editing procedures described previously.¹¹ The unit was set to take readings every 15 minutes through the 24 hours. The total number of ambulatory BP readings per patient was 107.4 (SD 12), and 89.6 (SD 11) readings per patient fulfilled editing criteria. Error percentage was 15.9% (SD 12).

ECHOCARDIOGRAPHIC METHODS: M-Mode echocardiograms were recorded under cross-sectional control using ATL Ultramark 8 and 9 systems (Advanced Technology Laboratories, Bellevue, Washington). LV measure-

TABLE II Relations of Casual and Average 24-Hour Ambulatory Blood Pressure to the Echocardiographic Indexes of Left Ventricular Structure

	All Subjects (n = 257)				Normotensives (n = 92)				Hypertensives (n = 165)			
	SBP		DBP		SBP		DBP		SBP		DBP	
	Casual	24-h	Casual	24-h	Casual	24-h	Casual	24-h	Casual	24-h	Casual	24-h
End-diastolic IVS thickness	0.40*	0.50*	0.37*	0.37*	0.20	0.31*	0.10	0.19	0.52*	0.46*	0.29*	0.28*
End-diastolic PW thickness	0.38*	0.53*	0.36*	0.43*	0.28*	0.46*	0.05	0.31*	0.26*	0.46*	0.27*	0.34*
LV mass	0.38*	0.52*	0.34*	0.42*	0.23	0.34*	0.02	0.23	0.30*	0.41*	0.28*	0.37*
LV mass index	0.43*	0.51*	0.34*	0.39*	0.32*	0.36*	0.006	0.20	0.35*	0.47*	0.28*	0.33*
Relative wall thickness	0.33*	0.44*	0.32*	0.34*	0.23	0.41*	0.08	0.28*	0.22*	0.36*	0.23*	0.22*
Cross-sectional area	0.41*	0.55*	0.37*	0.44*	0.25*	0.38*	0.05	0.25*	0.31*	0.51*	0.30*	0.37*
Cross-sectional area index	0.46*	0.53*	0.37*	0.39*	0.34*	0.40*	0.03	0.21	0.38*	0.47*	0.30*	0.30*

* p < 0.01.
DBP = diastolic blood pressure; IVS = interventricular septum; LV = left ventricular; PW = posterior wall; SBP = systolic blood pressure.

ments were obtained at end-diastole and end-systole according to the recommendations of the American Society of Echocardiography (ASE).¹⁸ LV mass was calculated using the following equation based on necropsy validation studies¹⁹: $LV\ mass = 0.80 \times [(ASE\text{-}cube\ LV\ mass)] + 0.6\ g$, and $ASE\text{-}cube\ LV\ mass = 1.04 \times [(IVSd + LVIDd + PWTd)^3 - LVIDd^3]$, where IVSd = interventricular septal thickness at end-diastole, LVIDd = LV internal dimension at end-dias-

tole, and PWTd = posterior wall thickness at end-dias-

tole. All echocardiographic examinations were performed by the same sonographer. Echocardiographic tracings were read in random order by 2 investigators who were unaware of the patients' casual and ambulatory BP levels. Both investigators marked locations on stop frames on the screen of the ATL Ultrasound System, and the mean values from ≥ 5 measurements for each param-

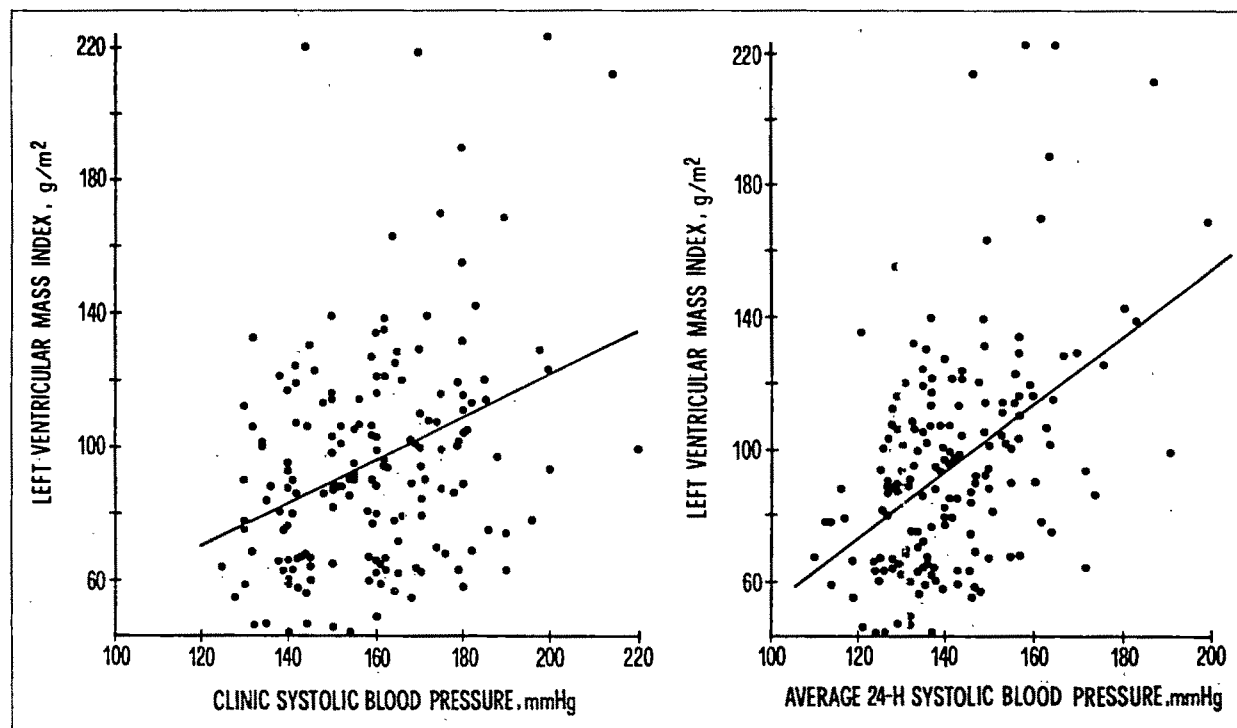


FIGURE 1. Relation of left ventricular mass index to casual (clinical) and average 24-hour ambulatory systolic blood pressure. See text for explanation.

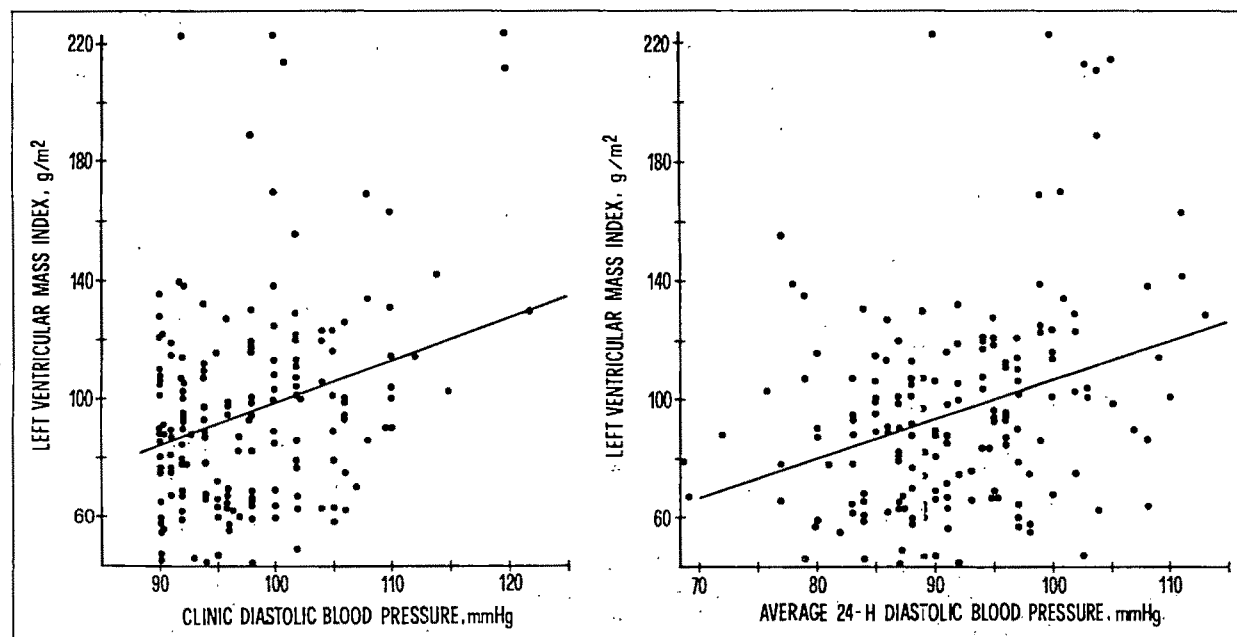


FIGURE 2. Relation of left ventricular mass index to casual (clinical) and average 24-hour ambulatory diastolic blood pressure. See text for explanation.

ter for observer were computed. Only frames with optimal visualization of LV interfaces and showing simultaneous visualization of IVS, PWT and LVID throughout the cardiac cycle were considered for reading. Relative wall thickness²⁰ and cross-sectional area²¹ were calculated as previously described. Fractional shortening was calculated according to the formula $[(LVIDd - LVIDs)/LVIDd] \times 100$.

STATISTICAL ANALYSIS: All data were stored by using the DBASE III software, and analyzed by using the SPSS/PC+ V2.0 package.²² One-way analysis of variance, nonparametric tests and multiple comparisons according to Tukey's test were used to compare the normotensive with the hypertensive group. The z statistics²³ were used to test the significance of differences between correlation coefficients, and the t statistics²⁴ to test parallelism of different regression lines. The 5% level of statistical significance was adopted for all tests.

RESULTS

Table I lists the statistical significance of differences between hypertensive patients and healthy normotensive subjects. Age, height, weight, sex prevalence and body surface area did not differ between the 2 groups. Casual and ambulatory heart rate were slightly higher in the hypertensive than in the normotensive group. Prevalence of LV hypertrophy (LV mass index >120 g/m²^{25,26}) was 7% in the normotensive and 17.6% in the hypertensive group. Within the latter group it was 14.8 and 30.0%, respectively, in patients with casual diastolic BP 90 to 104 mm Hg (n = 135) or ≥ 105 mm Hg (n = 30).

Relations of casual and ambulatory blood pressure to left ventricular structure: Table II lists the correlation coefficients of the echocardiographic indexes of LV structure to casual and ambulatory BP. In general,

there were weak correlations between casual or ambulatory BP readings and echocardiographic indexes of LV structure. However, all correlations in the normotensive and hypertensive groups were closer to the ambulatory than to the casual readings (all values $p < 0.05$, with the exception of the correlations between diastolic BP and septal thickness, relative wall thickness and cross-sectional area index, which showed nonstatistically dissimilar correlation coefficients between casual and ambulatory readings).

A plot of the relation of LV mass index to casual and average 24-hour systolic BP is shown in Figure 1. The relation of LV mass index to casual systolic BP was defined by the equation: LV mass index (g/m²) = $0.636 \times$ casual systolic BP (mm Hg) - 5.74 (standard error of the b coefficient [SEb] = 0.134). The relation of LV mass index to average 24-hour systolic BP was defined by the equation: LV mass index (g/m²) = $1.01 \times$ average 24-hour systolic BP (mm Hg) - 47.8 (SEb = 0.147). LV mass index increased more with average 24-hour than with casual systolic BP (parallelism test²⁴: $p < 0.05$). A plot of the relation of LV mass index to casual and average 24-hour diastolic BP is shown in Figure 2. The relation of LV mass index to casual diastolic BP was defined by the equation: LV mass index (g/m²) = $1.405 \times$ casual diastolic BP (mm Hg) - 41.78 (SEb = 0.375). The relation of LV mass index to average 24-hour diastolic BP was defined by the equation: LV mass index (g/m²) = $1.319 \times$ average 24-hour diastolic (mm Hg) - 25.23 (SEb = 0.297). LV mass index increased in a similar fashion to average 24-hour and casual diastolic BP (parallelism test²⁴: $p =$ difference not significant [NS]).

Risk stratification of left ventricular hypertrophy: Figure 3 shows the scatter plot of the relation of average 24-hour ambulatory or casual systolic BP in the hy-

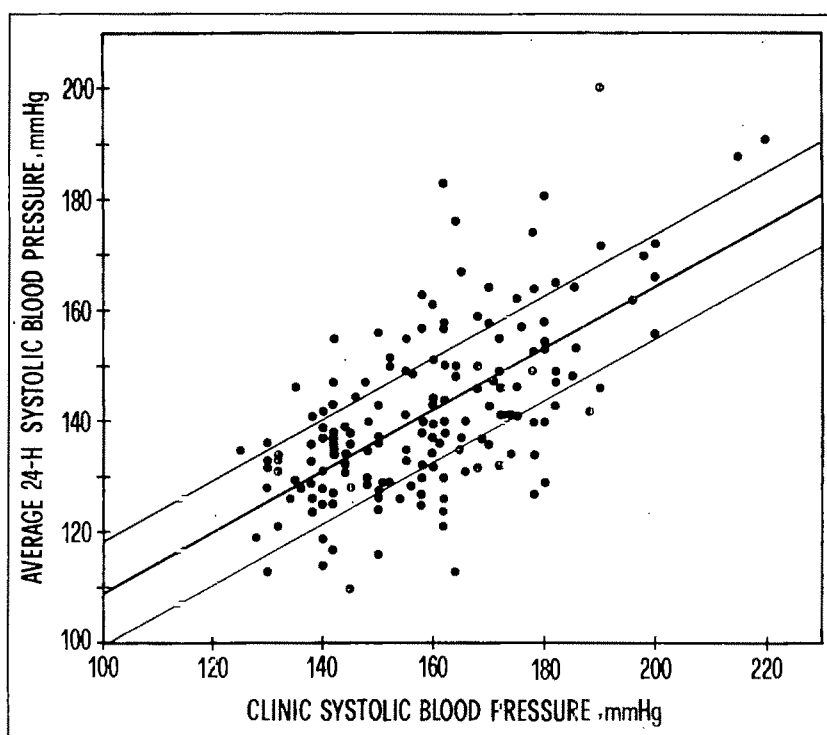


FIGURE 3. Relation of average 24-hour to casual (clinical) systolic blood pressure. The limit of 10 mm Hg above and below the regression line was used to generate groups of patients with ambulatory systolic blood pressure disproportionately high (≥ 10 mm Hg) or low (≤ 10 mm Hg) relative to casual blood pressure.

pertensive group. The relation was defined by the equation: Average 24-hour ambulatory systolic BP (mm Hg) = $54.16 + (0.55 \times \text{casual systolic BP [mm Hg]})$, SEb = 0.051, $r = 0.64$, $p < 0.001$.

The scatter plot of the relation of average 24-hour ambulatory to casual diastolic BP in the hypertensive group is shown in Figure 4. The relation was defined by the equation: Average 24-hour ambulatory diastolic BP (mm Hg) = $28.35 + (0.65 \times \text{casual diastolic BP [mm Hg]})$, SEb = 0.08, $r = 0.52$, $p < 0.001$.

Both figures show that average 24-hour BP in some patients fell notably above or below the regression line. Thus, according to the methodology used by Perloff et al,^{5,6} hypertensive patients were classified into 3 groups according to the difference between their observed and their predicted level (regression line) of ambulatory BP estimated from their casual BP. The "high" ambulatory BP group was defined by an average 24-hour systolic BP ≥ 10 mm Hg than predicted or by an average 24-hour diastolic BP ≥ 6 mm Hg than predicted. The "low" BP group was defined by an average 24-hour systolic BP ≤ 10 mm Hg than predicted or by an average 24-hour diastolic BP ≤ 6 mm Hg than predicted. The remaining patients, who had average 24-hour ambulatory BP within 9 mm Hg (systolic) or 5 mm Hg (diastolic) around the predicted level, were classified into an "intermediate" ambulatory BP group. Thirty-two, 102 and 31 patients, respectively, were classified into the low, intermediate and high BP groups based on ambulatory systolic BP (66, 71 and 68% of whom ($p = \text{NS}$) had never been treated), and 38, 93 and 34 patients were classified into the low, intermediate and high BP groups based on ambulatory diastolic BP (61, 70 and 67% of whom ($p = \text{NS}$) had never been treated). The main findings in the normotensive control subjects and hypertensive patients in the 3 groups are listed in Table III (systolic BP) and Table IV (diastolic BP). Whereas age did not differ between the groups, body surface area was slightly lower in the low ambulatory BP group compared with that in the other groups. Casual systolic and diastolic BPs were lower in the normotensive group compared with each of the hypertensive groups, but not dissimilar between the 3 hypertensive groups. Prevalence of men was higher in the high ambulatory BP groups (68% in both) compared with the intermediate (56% in both) and low (systolic 31%, diastolic 34%) BP groups (all $p < 0.01$).

LV mass and other indexes of LV structure increased in the high ambulatory BP groups, particularly when compared with indexes in the low and, to a lesser extent, intermediate BP groups. LV end-diastolic diameter and shortening fraction did not differ between groups. Prevalence of LV hypertrophy was 7% in the normotensive group, 6, 15 and 39% in the low, intermediate and high BP groups defined by systolic BP (chi-square = 22.5; $p < 0.0001$), and 10, 14 and 35% in the low, intermediate and high BP groups defined by diastolic BP (chi-square = 18.2; $p = 0.0004$). There were no statistical differences between the normotensive and low ambulatory BP groups in the echocardiographic indexes of LV structure, both in terms of absolute values and prevalence of LV hypertrophy. LV mass index was

higher in men than in women in the low ambulatory BP group defined by systolic (98 vs 75 g/m², $p < 0.05$) and diastolic (102 vs 83 g/m², $p < 0.05$) BP, but it did not differ between the genders in the high ambulatory BP group defined by systolic (116 vs 117 g/m², $p = \text{NS}$) and diastolic (117 vs 98 g/m², $p = \text{NS}$) BP. Electrocardiographic Romhilt-Estes score was ≥ 5 in 2 of 32, 5 of 102 and 5 of 31 patients, respectively, in the low, intermediate and high ambulatory BP groups defined by systolic BP, and in 2 of 38, 5 of 93 and 5 of 34 patients in the low, intermediate and high BP groups defined by diastolic BP, but none of the differences between the low and high BP groups yielded statistical significance (chi-square = 1.2 and 1.5, respectively, all $p = \text{NS}$).

DISCUSSION

The findings of this study clarify some clinical implications of the superiority of ambulatory over casual BP readings in predicting the degree of cardiac involvement in a large population of untreated and unselected hypertensive patients. In these patients, prevalence of echocardiographic LV hypertrophy was rather low (14.8% in those with mild hypertension and 30% in patients with casual diastolic BP ≥ 105 mm Hg), as reported in comparable hypertensive populations.^{27,28}

In agreement with previous studies using noninvasive^{8,9} or intraarterial¹⁰ BP monitoring, the correlation between LV mass and average 24-hour systolic or diastolic BP was closer than that between LV mass and casual BP. All correlations, however, were rather weak,

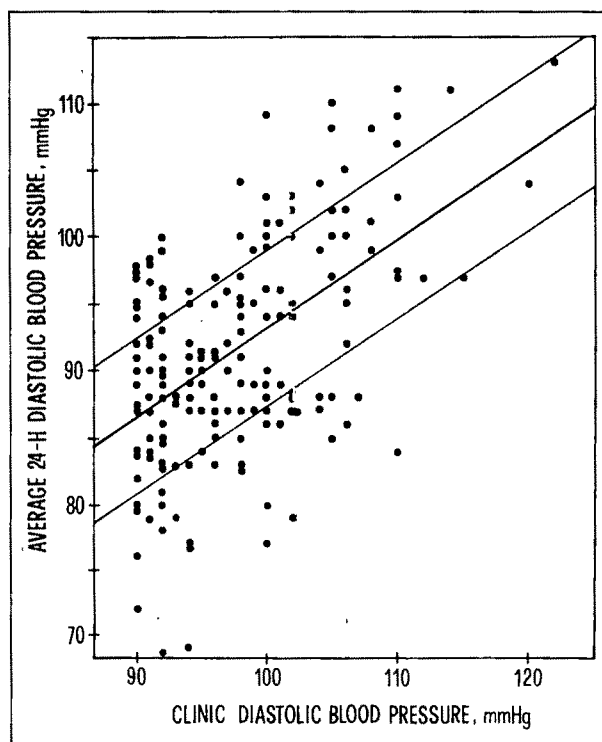


FIGURE 4. Relation of average 24-hour to casual (clinic) diastolic blood pressure. The limit of 6 mm Hg above and below the regression line was used to generate groups of patients with ambulatory diastolic blood pressure disproportionately high (≥ 6 mm Hg) or low (≤ 6 mm Hg) relative to casual blood pressure.

TABLE III Descriptive Findings, Casual and Ambulatory Blood Pressure and Echocardiographic Data in the Normotensive Group and in the "Low" (I), "Intermediate" (II) and "High" (III) Blood Pressure Groups Defined by the Difference Between Observed and Predicted Ambulatory Systolic Blood Pressure

Variable	Normotensive Subjects (n = 92)		Hypertensive Patients (n = 165)						ANOVA F p		Multiple Comparisons					
			I (n = 32)		II (n = 102)		III (n = 31)				Normo- tensives vs		I vs		II vs	
I		II		III		I	II	III	II	III	III					
Age (yrs)	50	(14)	52	(13)	52	(11)	54	(14)	0.7	NS						
Weight (kg)	73	(12)	66	(15)	76	(13)	80	(13)	6.8	*	NS	NS	*	*	*	NS
Height (cm)	168	(8)	162	(8)	167	(8)	169	(10)	3.6	*	NS	NS	†	†	NS	NS
BSA (m ²)	1.8	(0.2)	1.7	(0.2)	1.8	(0.2)	1.9	(0.2)	7.2	*	NS	NS	*	*	*	NS
Casual SBP (mm Hg)	136	(13)	163	(15)	157	(18)	163	(22)	42.1	*	*	*	*	NS	NS	NS
Casual DBP (mm Hg)	80	(7)	95	(6)	97	(6)	100	(8)	139.1	*	*	*	*	NS	NS	NS
Casual HR (beats/min)	73	(10)	75	(13)	77	(12)	76	(13)	2.1	NS						
Average 24-hour SBF (mm Hg)	123	(13)	125	(9)	140	(11)	161	(15)	81.7	*	NS	*	*	*	*	*
Average 24-hour DBP (mm Hg)	79	(8)	85	(7)	92	(7)	99	(8)	73.6	*	*	*	*	*	*	*
Average 24-hour HR (beats/min)	73	(6)	76	(8)	76	(8)	78	(8)	4.5	*	NS	†	†	NS	NS	NS
End-diastolic VS thickness (cm)	0.79	(0.2)	0.81	(0.2)	0.95	(0.3)	1.10	(0.4)	14.7	*	NS	*	*	*	*	*
End-diastolic PW thickness (cm)	0.71	(0.1)	0.72	(0.2)	0.82	(0.2)	0.95	(0.2)	19.1	*	NS	*	*	*	*	*
LV end-diastolic diameter (cm)	5.29	(0.6)	5.17	(0.7)	5.26	(0.6)	5.46	(0.7)	1.2	NS						
Shortening fraction (%)	40	(7)	39	(8)	39	(7)	37	(6)	1.7	NS						
LV mass (g)	139	(46)	141	(51)	172	(59)	223	(87)	18.0	*	NS	*	*	*	*	*
LV mass index (g/m ²)	77	(23)	82	(26)	93	(28)	117	(47)	16.1	*	NS	*	*	NS	*	*
Relative wall thickness	0.27	(0.07)	0.28	(0.07)	0.32	(0.08)	0.35	(0.10)	10.9	*	NS	*	*	NS	*	NS
Cross-sectional area (cm ²)	14.2	(3.6)	14.5	(3.9)	17.2	(4.6)	20.9	(6.7)	20.3	*	NS	*	*	*	*	*
Cross-sectional area index (cm ² /m ²)	7.9	(1.9)	3.48	(1.9)	9.36	(2.2)	11.06	(3.6)	16.2	*	NS	*	*	*	*	*

Data expressed as mean ± standard deviation.
I = ambulatory systolic blood pressure ≤10 mm Hg than predicted; II = ambulatory systolic blood pressure within 9 mm Hg of predicted; III = ambulatory systolic blood pressure ≥10 mm Hg than predicted.
ANOVA = analysis of variance; BSA = body surface area; DBP = diastolic blood pressure; HR = heart rate; LV = left ventricular; NS = not significant; PW = left ventricular posterior wall; SBP = systolic blood pressure; VS = ventricular septum; * = p < 0.05; † p < 0.05.

TABLE IV Descriptive Findings, Casual and Ambulatory Blood Pressure and Echocardiographic Data in the Normotensive Group and in the "Low" (I), "Intermediate" (II) and "High" (III) Blood Pressure Groups Defined by the Difference Between Observed and Predicted Ambulatory Diastolic Blood Pressure

Variable	Normotensive Subjects (n = 92)		Hypertensive Patients (n = 165)						ANOVA		Multiple Comparisons					
			I (n = 38)		II (n = 93)		III (n = 34)				Normo-tensives vs		I vs		II vs	
								F	p	I	II	III	I	II	III	
Age (yrs)	50	(14)	54	(11)	51	(12)	55	(12)	0.5	NS						
Weight (kg)	73	(12)	57	(13)	77	(14)	78	(13)	5.5	*	NS	NS	NS	†	†	NS
Height (cm)	168	(8)	153	(8)	168	(9)	168	(7)	3.8	*	NS	NS	NS	†	NS	NS
BSA (m ²)	1.8	(0.2)	1.7	(0.2)	1.9	(0.2)	1.9	(0.2)	6.0	*	NS	NS	NS	*	*	NS
Casual SBP (mm Hg)	136	(13)	150	(16)	157	(19)	164	(19)	41.9	*	*	*	*	*	NS	NS
Casual DBP (mm Hg)	80	(7)	98	(6)	97	(7)	98	(7)	137.1	*	*	*	*	*	NS	NS
Casual HR (beats/min)	73	(10)	76	(11)	78	(13)	76	(13)	2.3	NS						
Average 24-hour SBP (mm Hg)	123	(13)	131	(11)	141	(14)	156	(15)	54.9	*	†	*	*	*	*	*
Average 24-hour DBP (mm Hg)	79	(8)	82	(6)	92	(6)	101	(5)	123.3	*	NS	*	*	*	*	*
Average 24-hour HR (beats/min)	73	(6)	75	(9)	77	(8)	77	(8)	4.0	*	NS	†	†	NS	NS	NS
End-diastolic VS thickness (cm)	0.79	(0.2)	0.90	(0.2)	0.95	(0.3)	1.03	(0.3)	9.4	*	NS	*	*	NS	†	NS
End-diastolic PW thickness (cm)	0.71	(0.1)	0.79	(0.2)	0.81	(0.2)	0.90	(0.2)	11.9	*	NS	*	*	NS	*	*
LV end-diastolic diameter (cm)	5.29	(0.6)	5.14	(0.6)	5.27	(0.6)	5.46	(0.7)	1.6	NS						
Shortening fraction (%)	40	(7)	39	(3)	38	(7)	40	(5)	2.0	NS						
LV mass (g)	139	(46)	158	(51)	172	(64)	210	(88)	12.3	*	NS	*	*	NS	*	*
LV mass index (g/m ²)	77	(23)	90	(26)	92	(31)	111	(43)	11.5	*	NS	*	*	NS	*	*
Relative wall thickness	0.27	(0.07)	0.29	(0.09)	0.31	(0.08)	0.34	(0.09)	6.9	*	NS	*	*	NS	†	NS
Cross-sectional area (cm ²)	14.2	(3.6)	15.0	(4.1)	17.1	(5.1)	14.8	(6.4)	13.0	*	NS	*	*	NS	*	*
Cross-sectional area index (cm ² /m ²)	7.9	(1.9)	8.67	(2.2)	9.20	(2.5)	10.56	(3.3)	11.8	*	NS	*	*	NS	*	*

* p < 0.01; † p < 0.05.

Data expressed as mean ± standard deviation.

I = ambulatory diastolic blood pressure ≤6 mm Hg than predicted; II = ambulatory diastolic blood pressure within 5 mm Hg of predicted; III = ambulatory diastolic blood pressure ≥6 mm Hg than predicted.

Abbreviations as in Table III.

and no more than 25% of variability in the echocardiographic indexes of LV structure could be accounted for by the relation with either ambulatory or clinical BP. The weakness of these correlations supports the view^{29,30} that several factors besides BP, including hemodynamic load and myocardial contractility,³¹ are probably involved in the development of LV hypertrophy in human hypertension.

Prediction of the degree of cardiac hypertrophy:

Because correlation coefficients measure only the closeness of an association between 2 variables, a significant difference between 2 correlation coefficients does not imply, in our case, that the echocardiographic measurements of LV structure are predicted differently by ambulatory than by casual BP. To clarify this point, we compared the slope of the 2 regression lines and found that the predicted value of LV mass index increased more with ambulatory than with casual systolic BP, and increased to a comparable extent with ambulatory and casual diastolic BP. Thus, the same systolic BP level predicted a higher mean value of LV mass if it was the average of about 90 noninvasive readings throughout the 24 hours, and predicted a lower mean value of LV mass if it was a casual reading. By contrast, the same level of ambulatory or casual diastolic BP predicted comparable values of LV mass. Ambulatory systolic BP was thus superior to ambulatory diastolic BP in terms of advantage over casual BP in the prediction of the echocardiographic measurements of LV structure in hypertension.

Clinical implications: The high long-term morbidity and mortality in hypertensive patients with ambulatory BP significantly higher than predicted^{5,6} has been interpreted as an effect of greater cardiovascular load throughout 24 hours in these patients (thus producing higher long-term risk) than in patients with similar casual but lower ambulatory BP levels. These epidemiologic findings suggest that casual and ambulatory BP readings are not alternative but complementary tools to assess the risk in an individual patient.

In this study, LV mass and other echocardiographic indexes of cardiac hypertrophy were increased in patient with disproportionately high ambulatory BP compared with patients in the low ambulatory BP group. The prevalence of LV hypertrophy, which did not differ between the normotensive and the low ambulatory BP groups, increased by more than fourfold from the low to the high ambulatory BP group. There were more women in the low than in the high ambulatory BP group, in agreement with the findings of Pickering et al³² who showed a higher prevalence of women among subjects with "white-coat hypertension" (i.e., normal daytime ambulatory BP despite clinical hypertension); this could explain part of the variation of LV mass between the 3 ambulatory BP groups. In fact, LV mass seems to be lower in hypertensive women than in men,²⁶ at least before menopause.³³ In our study, LV mass was lower in women than in men in the group at lower risk of LV hypertrophy, but did not differ between the genders in the group at higher risk of LV hypertrophy.

Prevalence of LV hypertrophy by electrocardiography was low, as noted in comparable patient populations,³⁴ and not enough to differentiate the high from the low ambulatory BP groups. This is probably due to the lower sensitivity of electrocardiography in comparison with echocardiography in detecting LV hypertrophy proved at necropsy.³⁵

The findings of this study suggest that one possible reason for the prognostic value of noninvasive ambulatory BP readings, as it has been reported,^{5,6} may be the stratification of patients into subsets at different risk of echocardiographically determined LV hypertrophy, an independent prognostic marker.¹²⁻¹⁵

A practical clinical implication of our findings is that a thorough echographic examination of the left ventricle should be recommended in hypertensive patients with ambulatory BP disproportionately high relative to casual BP, and classified in the high ambulatory BP group. Conversely, echocardiography is probably of little clinical importance in hypertensive patients with ambulatory BP disproportionately low relative to casual BP and classified in the low ambulatory BP group. In these patients, LV mass index and other indexes of LV hypertrophy are likely to be within the normal range. These conclusions are supported by a recent study by White et al,³⁶ who showed that in patients who were found to be hypertensive in the physician's office, but normotensive on the basis of noninvasive ambulatory BP monitoring, LV mass index was not different from that of normotensive control subjects, and lower than in patients with higher ambulatory BP values.

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Cardiac and Skeletal Muscle Adaptations to Training in Systemic Hypertension and Effect of Beta Blockade (Metoprolol or Propranolol)

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Cardiovascular and peripheral adaptations to an aerobic conditioning program were studied in 30 hypertensive adults taking either placebo, β_1 -selective β -adrenergic blocker (metoprolol) or β_1 -nonselective β -adrenergic blocker (propranolol). The placebo group increased aerobic capacity ($\dot{V}O_2\text{max}$) 24% ($p < 0.002$), largely explained by an increased peripheral arteriovenous (AV) oxygen difference with minimal changes in cardiac size and function. Resting blood pressure and total systemic resistance also decreased. The group taking a β_1 -selective β blocker increased $\dot{V}O_2\text{max}$ 8% ($p < 0.05$), reduced resting blood pressure but had no significant change of AV oxygen difference or cardiac size or function. The group taking the β_1 -nonselective β blocker propranolol had no increase in $\dot{V}O_2\text{max}$, no decrease in resting blood pressure and no cardiovascular or peripheral adaptations to the exercise program. Thus, β_1 -selective and β_1 -nonselective β blockers attenuate conditioning in hypertensive patients to differing degrees, in each case by blocking peripheral mechanisms of conditioning.

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Beta-adrenergic blocking agents have been demonstrated in most studies to exert significant negative effects on acute exercise capacity and conditioning response to an aerobic exercise program in healthy subjects.¹⁻⁵ Maximum voluntary exercise time and aerobic capacity are diminished and exercise conditioning related adaptations are attenuated. Studies of exercise conditioning in hypertensive patients demonstrate an increased aerobic capacity along with a generally reduced resting blood pressure.⁶⁻⁸ Because β -adrenergic blocking agents are first-line drugs for the therapy of arterial hypertension,⁹ we tested the hypothesis that β -adrenergic blockers also exert negative effects on the exercise conditioning response in hypertensives, with special attention to cardiac and peripheral adaptations. Because β_1 -selective blockade may preserve β_2 receptor-mediated vasodilation and substrate availability during exercise, effects of the selective agent metoprolol were compared to the nonselective agent propranolol.

METHODS

Patients: Thirty-one hypertensive adults, aged 30 to 55 years (mean \pm standard deviation 46.5 ± 7) were recruited. Resting seated blood pressure was determined by cuff sphygmomanometry. Nine values obtained on separate days were averaged. Screening was performed at least 2 weeks after discontinuation of any antihypertensive drugs. All subjects had either a diastolic pressure ≥ 95 mm Hg, a systolic pressure ≥ 145 mm Hg or systolic and diastolic pressures both $\geq 140/90$ (mean $145 \pm 5/95 \pm 4$). All subjects were sedentary nonsmokers and had normal hematocrits. A preliminary maximal treadmill exercise test with electrocardiographic monitoring and expired gas analysis familiarized subjects with the apparatus. Subjects were randomized into 3 groups of similar fitness, blood pressure, body weight and male/female ratio (Table I).

Baseline studies: Before drug therapy, subjects underwent baseline fitness testing on the treadmill in addition to specific assessments of cardiac size and function and a muscle biopsy determination of skeletal muscle oxidative enzyme activity. Aerobic exercise capacity was determined by having subjects perform exercise to exhaustion on the treadmill using a modified Balke protocol,¹⁰ with expired gas analyzed at 30-second intervals by a Sensormedics Horizon metabolic measurement cart (Anaheim, California). Exercise was terminated at exhaustion in all 31 subjects. In all cases this was associ-

TABLE I Baseline Subject Characteristics

	Placebo	Metoprolol	Propranolol
Age (yr)	43 ± 2	46 ± 2	47 ± 2
Male/female	7/3	7/3	8/2
Weight (kg)	87.7 ± 5	86.8 ± 6	85.2 ± 4
Blood pressure	146/95 ± 7/2	144/93 ± 4/6	144/95 ± 4/4
$\dot{V}O_2$ max (ml/kg/min)	30.2 ± 8	32.1 ± 8	34.1 ± 8
RER	1.12 ± 0.10	1.13 ± 0.06	1.11 ± 0.05

Values are mean ± standard deviation.
RER = respiratory equivalence ratio = $\dot{V}CO_2 \div \dot{V}O_2$; $\dot{V}O_2$ max = maximal oxygen consumption.

ated with a respiratory equivalence ratio ($\dot{V}O_2 \div \dot{V}CO_2$) >1.00 (mean 1.12 ± 0.07). No subjects stopped for chest pain, electrocardiographic ischemia, cardiac arrhythmia or extreme hypertensive response (≥ 250 mm Hg systolic).

Cardiac studies included a rest and exercise hemodynamic evaluation using carbon dioxide (CO_2) rebreathing technique (seated and during treadmill exercise) for determination of cardiac output, a resting M-mode echocardiographic evaluation (in the left lateral decubitus position) and measurement of systolic time intervals. The CO_2 rebreathing technique has been validated against invasive techniques (Fick, thermodilution); correlations are excellent at rest and even better during exercise.¹¹⁻¹⁴ In our laboratory the standard deviation of within-subject variability is 0.58 liters/min and the coefficient of variation is 10% for resting cardiac output.¹⁵ During exercise, these values are 0.87 liters/min and 6%. Cardiac outputs were determined in triplicate both at rest and during steady-state exercise at 5-minute intervals at an intensity of 70% of the previously determined maximal oxygen consumption ($\dot{V}O_{2max}$). Derived values include stroke volume (cardiac output \div heart rate), cardiac index, arteriovenous (AV) oxygen difference (oxygen consumption \div cardiac output) and total systemic resistance in dynes-cm⁻⁵ [mean blood pressure $\times 80 \div$ (cardiac output)].

Echocardiographic, phonocardiographic and carotid displacement tracings were recorded by the same technician using an Irex II system. Left ventricular M-mode dimension data were obtained and analyzed according

to the recommendations of the American Society of Ultrasound.¹⁶ Left ventricular volumes were calculated using the Teichholtz formula¹⁷ and left ventricular mass by the cube method of Devereux and Reichek.¹⁸ Systolic time intervals were recorded and measured using the methodology of Weissler and Garrard.¹⁹ All data were measured from 3 successive cardiac cycles by 2 observers independently and a consensus determined.

Skeletal muscle studies: Skeletal muscle biopsy samples were obtained from the vastus lateralis muscle at rest using a closed-needle technique. Mean sample wet weight was 34 mg. Samples were frozen at $-20^\circ C$ for biochemical analysis. Succinyl dehydrogenase activity was determined by a modification of the method of Cooperstein et al²⁰ and expressed as enzyme units (micromole substrate converted per minute) per mg protein. Carnitine palmityl transferase was measured by a method patterned after that of Hoppel and Tomec.²¹ Activity was determined on 0.1 ml of homogenate in a reaction volume of 1.0 ml for 30 minutes at $30^\circ C$. The reaction mixture contained 500 mM tris-chloride buffer at pH 7.4, 500 mM hydroxylamine, 5 mM glutathione, 0.6 mM palmityl carnitine and 2 mM coenzyme A. A unit of activity corresponds to production of 1 nmole of product per minute.

After baseline testing, subjects began therapy in a double-blinded randomized fashion with either propranolol 80 mg, metoprolol 100 mg or placebo, each taken twice daily. The maximal stress test and the cardiac output determinations were repeated after 1 week of drug therapy. Equivalence of β -blocking effect was confirmed by a similar decrement of maximal exercise tachycardia (-44 beats/min with metoprolol, -48 beats/min with propranolol, $p =$ not significant [NS]).

Training protocol: Subjects performed a 10-week training protocol of treadmill and bicycle exercise. They exercised 4 times weekly with sessions consisting of 30 minutes of electrocardiographically monitored treadmill exercise, 15 minutes of bicycle ergometry and 5 minutes of rowing as well as warm up and cool down. Intensity was monitored to keep heart rate at 75 to 85% of maximal measured heart rate with the drug. The 3 groups trained at similar exercise intensities, extrapolated from training heart rates on the treadmill, averaging 70.3% of

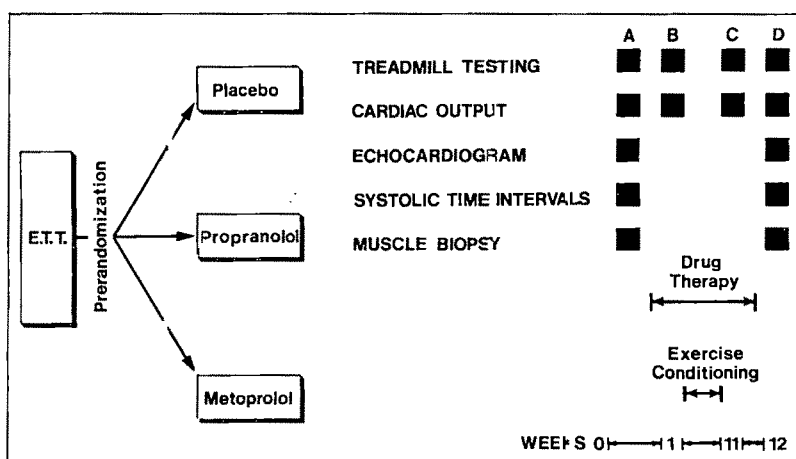
**FIGURE 1.** Study flow diagram. E.T.T. = exercise treadmill test.

TABLE II Acute Effects of Beta-Adrenergic Blockade

	Placebo		Metoprolol		Propranolol	
	Predrug	Drug	Predrug	Drug	Predrug	Drug
Resting heart rate (beats/min)	75 ± 14	79 ± 12*	85 ± 13	64 ± 9†	81 ± 10	61 ± 8†
Blood pressure (mm Hg)	146/95 ± 7/2	138/89 ± 14/8	144/93 ± 4/6	127/83 ± 18/13	144/95 ± 4/4	125/78 ± 13/9†
Cardiac output						
Rest (liters/min)	4.6 ± 0.8	4.9 ± 0.9*	5.4 ± 1.1	4.8 ± 0.6†	5.3 ± 0.8	4.9 ± 0.8†
Exercise (0.7 $\dot{V}O_2$ max)	13.0 ± 3.0	12.1 ± 3.0	13.9 ± 2.5	12.7 ± 2.7†	13.5 ± 2.4	12.2 ± 2.6†
Exercise heart rate (beats/min)	126 ± 24	125 ± 22	134 ± 26	102 ± 21	129 ± 23	101 ± 18
Stroke volume (ml)						
Rest	61 ± 16	64 ± 15	65 ± 14	80 ± 18†	71 ± 19	93 ± 15†
Exercise (0.7 $\dot{V}O_2$ max)	103 ± 23	97 ± 21	104 ± 17	124 ± 22	105 ± 20	121 ± 21†

* $p < 0.05$ compared to other 2 drug groups.† $p < 0.05$ compared to pre-drug values are mean ± standard deviation. $\dot{V}O_2$ max = maximal oxygen consumption.

baseline $\dot{V}O_2$ max. After training, groups were retested with and without the drug as demonstrated on the study flow diagram (Figure 1). One subject was withdrawn from the protocol because of uncontrolled hypertension (>170 mm Hg) with drug therapy (placebo). The remaining 30 subjects attended 95% of the sessions.

Data analysis: Intergroup comparisons before and after training were obtained by a 2-way analysis of variance with the Scheffé correction for multiple comparisons. Intragroup comparisons before and after training used Student's t test for paired values.

RESULTS

Drug effects before conditioning: EXERCISE PERFORMANCE: The short-term effects of selective and nonselective β -blockade on exercise performance were assessed after 1 week of therapy and have been reported previously.⁶ Propranolol diminished $\dot{V}O_2$ max by 13% compared with baseline ($p < 0.05$). This effect differed from the effects of metoprolol (-3% , $p = \text{NS}$) and placebo ($+4\%$, $p = \text{NS}$) (Figure 2). Exercise duration diminished with propranolol from 17.2 ± 4 to 16.0 ± 3 minutes, which differed from the slight increase in treadmill

time noted with placebo and metoprolol ($p < 0.05$). Neither β blocker affected peak respiratory equivalence ratio (metoprolol 1.13 ± 0.06 to 1.13 ± 0.11 , propranolol 1.11 ± 0.05 to 1.08 ± 0.05 , both $p = \text{NS}$).

Hemodynamics: Both propranolol and metoprolol diminished resting systolic and diastolic blood pressure compared with placebo (Table II). Resting cardiac output was diminished with propranolol ($p < 0.05$) and with metoprolol ($p < 0.05$) compared with the baseline measure before drug administration, and these changes with each drug differed from the effect of placebo ($p < 0.02$). Exercise cardiac output measured at an exercise intensity of 70% of predrug $\dot{V}O_2$ max was diminished by each β blocker compared with the predrug evaluation ($p < 0.05$). Stroke volume at rest was increased from baseline with metoprolol ($p < 0.05$) and propranolol ($p < 0.05$) but not with placebo ($p = \text{NS}$). Total systemic resistance was unaffected by either of the drug therapies. During exercise, stroke volume was higher with each β blocker than that before the drug and compared with placebo. However, cardiac output during exercise was diminished in each of the β -blocking groups.

FIGURE 2. Maximal oxygen consumption ($\dot{V}O_2$ max) before and after exercise conditioning. E.T.T. = exercise treadmill testing. (Reproduced with permission from *Ann Intern Med.*⁶)

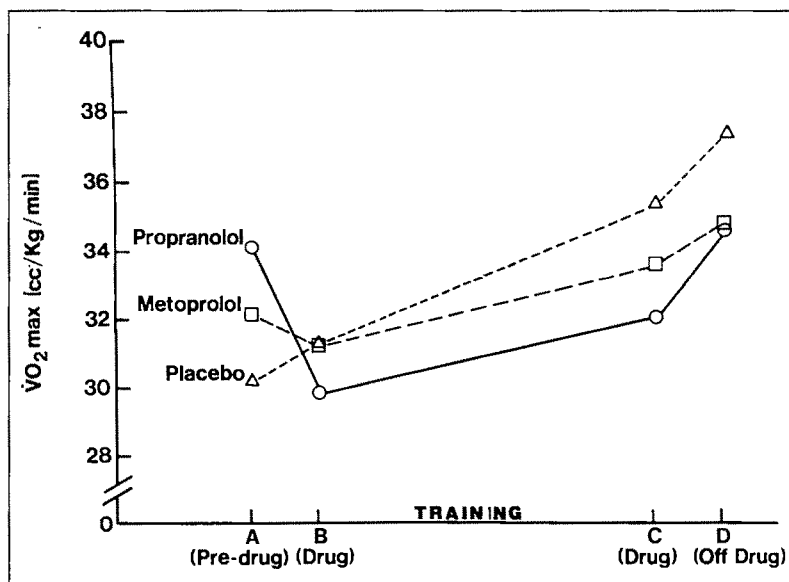


TABLE III Effects of Beta-Adrenergic Blockade After Conditioning

	Placebo		Metoprolol		Propranolol	
	A	D	A	D	A	D
Resting heart rate (beats/min)	75 ± 14	66 ± 17*	85 ± 13	90 ± 12	81 ± 10	87 ± 12
Blood pressure (mm.Hg)	146/95 ± 7/2	135/87 ± 13/7*	144/93 ± 4/6	133/87 ± 9/7*	144/95 ± 4/4	144/92 ± 4/11
$\dot{V}O_2$ max (ml/kg/min)	30.2 ± 8	27.4 ± 11*	32.1 ± 8	34.8 ± 7*	34.1 ± 7	34.7 ± 9 [†]
Cardiac output (liter/min)						
Rest	4.6 ± 0.8	5.2 ± 0.15	5.3 ± 0.8	5.4 ± 1.4	5.4 ± 1.1	5.7 ± 1.2
Exercise (0.7 $\dot{V}O_2$ max)	13.0 ± 3	11.4 ± 1.7*	13.9 ± 2.5	13.0 ± 2.6	13.5 ± 2.4	13.1 ± 2.4
Exercise heart rate (beats/min)	126 ± 24	109 ± 21	134 ± 26	131 ± 21	129 ± 23	125 ± 19
Stroke volume (ml)						
Rest	61 ± 16	77 ± 22*	65 ± 14	68 ± 23	71 ± 19	72 ± 21
Exercise (0.7 $\dot{V}O_2$ max)	103 ± 23	105 ± 20	104 ± 17	99 ± 16	105 ± 20	105 ± 20
Arteriovenous O ₂ diff (ml/100 ml)	13.8 ± 1.2	15.6 ± 2.2 [‡]	13.1 ± 2.3	13.4 ± 1.4	14.4 ± 1.3	14.3 ± 1.5
Exercise $\dot{V}O_2$	18 ± 4	18 ± 3	18 ± 4	17 ± 3	19 ± 3	19 ± 2

* p < 0.05 vs preconditioning.

† p < 0.05 vs other 2 groups.

‡ p < 0.05 vs placebo.

Values are mean ± standard deviation.

A = preconditioning, predrug; D = postconditioning, postdrug; diff = difference; other abbreviations as in Table I.

Effect of beta blockers on conditioning response:

EXERCISE PERFORMANCE: The placebo group improved maximal aerobic capacity from by 24% from test A to test D ($p < 0.002$) (Figure 2, Table III). The metoprolol group improved aerobic capacity 8% ($p < 0.05$), whereas the propranolol group showed no overall improvement in aerobic fitness ($p = \text{NS}$). The increase in $\dot{V}O_2$ max in the placebo group was significantly greater than the changes in propranolol ($p < 0.05$) with the metoprolol intermediate group ($p = \text{NS}$ vs placebo or propranolol). Exercise duration increased in all 3 groups from test A to test D with treadmill duration increasing 6.1 minutes with placebo, 4.7 minutes with metoprolol and 2.9 minutes with propranolol. These differences between groups were not significant. When exercise performance was assessed before drug withdrawal (test C), $\dot{V}O_2$ max increased 17% with placebo ($p < 0.01$) with a 4% increase noted with metoprolol ($p = 0.19$) and a 5% decrease with propranolol ($p = 0.24$). The change in the placebo group differed from the propranolol group ($p < 0.05$). For the entire study group, men ($n = 22$) and women ($n = 8$) trained to a similar degree, with men increasing $\dot{V}O_2$ max by 12% and women by 7% ($p = \text{NS}$).

Hemodynamics: Resting systolic blood pressure, measured at time D, after drug withdrawal, decreased significantly in both the placebo and metoprolol groups ($p < 0.05$) in contrast to the propranolol group ($p = \text{NS}$) (Table II). Diastolic pressure decreased with placebo ($p < 0.01$) and metoprolol ($p < 0.01$), with no change with propranolol ($p = \text{NS}$ between groups). Maximal heart rate and heart rate-systolic blood pressure product were unchanged in the 3 groups, with drugs, after conditioning. Submaximal (70% $\dot{V}O_2$ max) heart rate and heart rate-systolic blood pressure product both decreased in the placebo group and in the metoprolol group after conditioning but not in the propranolol group.

Resting cardiac output measured by the CO_2 re-breathing technique did not change in either of the 3 groups with conditioning, after drug withdrawal. How-

ever, in the placebo group, the determinants of cardiac output were altered by conditioning in that resting heart rate was lower (75 ± 14 to 66 ± 17 beats/min, $p < 0.05$) and stroke volume was higher (61 ± 16 to 77 ± 22 ml/min, $p < 0.05$). Resting heart rate and stroke volume were unaffected by conditioning in both β -blocking groups. The higher stroke volume at rest in the placebo group did not translate into a higher end-diastolic volume with echocardiography. Total systemic resistance at rest was diminished after conditioning in the placebo group ($1,899 \pm 465$ to $1,561 \pm 388$ dynes-cm⁻⁵, $p < 0.02$) but not in the metoprolol group ($1,684 \pm 307$ to $1,587 \pm 415$, $p = \text{NS}$) or in the propranolol group ($1,599 \pm 419$ to $1,465 \pm 276$, $p = \text{NS}$).

Exercise cardiac output measured at identical work loads at time A and time D (0.7 $\dot{V}O_2$ max from test A) diminished in the placebo group ($p < 0.03$) associated with an increased AV oxygen difference ($p < 0.05$). Exercise cardiac output was unchanged at time D with metoprolol and propranolol with no change in peripheral oxygen extraction. The diminished cardiac output during exercise in the placebo group was mediated entirely by a diminished heart rate (127 ± 14 to 110 ± 8 beats/min, $p < 0.05$) as exercise stroke volume was unchanged with conditioning 103 ± 0.23 to 105 ± 0.20 ml/min.

Cardiac size and function: ECHOCARDIOGRAPHIC STUDIES: M-mode echocardiographic studies were performed at rest in all subjects before and after conditioning, without medication. Left ventricular end-diastolic dimensions, end-systolic dimension, septal thickness, posterior wall thickness, fractional shortening and mass were all unchanged following conditioning in the 3 training groups (Table IV). Only 2 of the 31 subjects had an increased wall thickness (> 1.1 cm) before conditioning, with left ventricular masses of 325 and 259 g, respectively.

Systolic time intervals were performed at rest before and after conditioning without drugs as an index of left ventricular function. Neither the pre-ejection period, the

TABLE IV Echocardiographic Measures and Systolic Time Intervals

	Placebo		Metoprolol		Propranolol	
	A	D	A	D	A	D
LVIDd (mm)	54 ± 3	53 ± 3	51 ± 5	51 ± 3	51 ± 3	53 ± 4
LVIDs (mm)	34 ± 4	34 ± 3	33 ± 4	32 ± 4	34 ± 5	33 ± 3
IVS (mm)	9 ± 1	9 ± 0.7	9 ± 2	8 ± 0.8	10 ± 2	9 ± 0.9
LVPW (mm)	9 ± 0.8	9 ± 0.9	8 ± 0.5	8 ± 0.7	9 ± 1.5	9 ± 1
FS (%)	38 ± 5 [†]	37 ± 5	36 ± 7	37 ± 8	35 ± 8	38 ± 5
LV mass (g)	207 ± 35	204 ± 26	182 ± 35	165 ± 10	211 ± 58	204 ± 44
Systolic time intervals						
PEP (ms)	97 ± 19	104 ± 10	99 ± 20	97 ± 15	100 ± 18	99 ± 15
LVET (ms)	303 ± 25	308 ± 20	294 ± 24	311 ± 23	291 ± 19	293 ± 25
PEP ÷ LVET	32 ± 7	34 ± 4	33 ± 10	32 ± 5	35 ± 7	31 ± 5

None of the postconditioning values was significant at $p < 0.05$ level.

IVS = interventricular septal thickness; LVET = left ventricular ejection time; LVFS = fractional shortening (%); LVIDd = left ventricular internal dimension, diastole; LVIDs = left ventricular internal dimension, systole; LVPW = left ventricular posterior wall thickness; PEP = pre-ejection period; other abbreviations as in Table III.

ejection time nor the ratio was altered by conditioning in either of the 3 training groups (Table IV).

Skeletal muscle oxidative enzyme activity: Muscle biopsy specimens adequate for biochemical analysis of succinyl dehydrogenase activity were obtained in 19 patients. Carnitine palmitoyl acyl transferase activity was also measured in 27 patients. For the subgroup of 19 patients, succinyl dehydrogenase activity, expressed as enzyme units/mg protein, increased by 26% (0.88 ± 0.30 to 1.10 ± 0.55 , $p < 0.07$). In the individual drug groups, succinyl dehydrogenase activity increased by 27% with placebo (0.96 ± 0.43 to 1.22 ± 0.66 enzyme units/mg protein, $p = 0.20$, $n = 6$), by 41% with metoprolol (0.84 ± 0.42 to 1.18 ± 0.67 enzyme units/mg protein, $p < 0.07$, $n = 7$) and by 5% on propranolol (0.84 ± 0.14 to 0.88 ± 0.22 enzyme units/mg protein, $p = \text{NS}$, $n = 6$). Intergroup changes in enzyme activity were not significant between groups.

For the group of 27 patients, carnitine palmitoyl transferase activity was not significantly changed after exercise conditioning (4.94 ± 1.4 to 4.43 ± 1.2 Eu/mg protein, both $p = \text{NS}$), nor were there significant changes in enzyme activity in any of the 3 groups.

DISCUSSION

Most previous studies of exercise conditioning in hypertensive patients have documented an increased VO_2max and a reduced resting blood pressure.^{7,8} In nonhypertensive adults cardiac adaptations to conditioning include an increased left ventricular internal diameter and an increased left ventricular mass.^{22,23} Furthermore, studies in healthy adults have documented an increased skeletal muscle oxidative enzyme activity,²⁴ an increased local blood flow and vascular conductance during exercise,²⁵ and an increased capacity to extract and utilize oxygen peripherally.²⁶ Thus, normal subjects manifest both cardiac and peripheral adaptations to endurance exercise.

Effects of the conditioning program, per se, independent of drug effects, were studied in our middle-aged hypertensive group receiving placebo therapy. Maximal oxygen consumption increased by 24%, mediated almost entirely by an increased peripheral AV oxygen differ-

ence since exercise stroke volume and maximal heart rate did not increase with conditioning. Resting and exercise systolic blood pressure and resting diastolic blood pressure were decreased by the conditioning program as was submaximal exercise heart rate. Skeletal muscle succinyl dehydrogenase enzyme activity showed a trend toward increased activity. Thus, during high-intensity submaximal exercise, cardiac work is diminished after conditioning due to an enhanced peripheral extraction and utilization of oxygen.

The relative lack of training-induced changes in stroke volume and echocardiographic measures of internal cardiac dimensions and left ventricular mass in our placebo group differs from prior studies of conditioning in healthy adults. Studies in both younger healthy adults^{23,27} and in middle-aged patients with coronary artery disease^{28,29} document increases in resting left ventricular internal dimensions and stroke volume, both at rest and during exercise. Whereas only 2 of 31 hypertensive patients had left ventricular hypertrophy documented by echocardiography at baseline, abnormalities of diastolic filling patterns are common in hypertensives, even in the absence of hypertrophy.³⁰ Moreover, aging causes a decrease in left ventricular compliance.³¹⁻³³ The diastolic enlargement seen after an exercise conditioning program appears to be related to both an increased blood volume, and to a resting bradycardia.³⁴ Since our hypertensive subjects did exhibit a decrease in resting heart rate, our results suggest that, in contrast to nonhypertensives, either exercise-induced volume expansion does not occur or diastolic abnormalities limit the left ventricular dilation seen with training.

The mechanism of the increased peripheral utilization of oxygen seen in our placebo group is not clear. Whereas skeletal muscle oxidative enzyme activity showed a trend to an increased activity, changes in vascular conductance, skeletal muscle capillarity or intercellular oxygen diffusion could also have played important roles in improving substrate availability.

Beta-adrenergic blocking drugs are first-line agents for the treatment of systemic hypertension. In healthy subjects, they have been demonstrated to exert significant negative acute effects on VO_2max and exercise ca-

capacity and on the response to an aerobic conditioning program.¹⁻⁴ In a study by Wolfel et al,⁴ examining the mechanism of the diminished training response on β_1 -selective and nonselective β blockers, no measurable attenuation by a β blocker of training-induced skeletal muscle adaptations was seen. These include increases in oxidative enzymes, capillary supply and decreases in exercise blood lactate. Measures of cardiac output or overall peripheral oxygen extraction (AV oxygen difference), however, were not performed.

The conditioning effects noted in our hypertensive group taking the β_1 -selective agent metoprolol were different from those noted in the placebo group. Maximal oxygen consumption increased, but only by 8% ($p = \text{NS}$ vs placebo) and resting systolic and diastolic blood pressures were reduced. However, there were no conditioning-induced changes in resting stroke volume, or in measures of resting cardiac anatomy or function. As in the placebo group, skeletal muscle succinyl dehydrogenase activity showed a trend toward higher activity after conditioning. In contrast, the propranolol group did not demonstrate any training effects at all, as assessed by changes in aerobic capacity, stroke volume, cardiac dimensions, cardiac function or skeletal muscle enzymatic activity. The major difference between the 2 β -blocking groups and the placebo group was that peripheral extraction and utilization of oxygen was unaltered in the β -blocking groups.

Potential limitations of this study include the fact that there were a relatively small number of patients per group and the results may be specific to the doses of drugs utilized and the duration of exercise training performed. Conceivably, the β -blocking groups could have trained more with a longer duration program. It is also difficult to explain the discrepancy between echocardiographic and CO_2 rebreathing measures of end-diastolic dimensions and stroke volume in our placebo group. Additional study of the effect of training on heart size and stroke volume and their determinants would appear indicated.

The mechanism of the differing effects of selective and nonselective β blockers could relate to vasodilatory effects of partial β_2 stimulation, leading to a relatively increased local blood flow to exercising muscle. Metabolic effects of nonselective β blockers, which limit mobilization of free fatty acids and glucose during exercise, may also explain the differential effects observed.³⁵

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Pattern of Peripheral Venous Response to Volume Expansion in Borderline Systemic Hypertension

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An increased venous tone responsible for changes in systemic hemodynamics has been described in borderline hypertensive patients along with the release, in response to intravenous sodium chloride, of an endogenous sodium ion/potassium ion adenosine triphosphatase (Na^+/K^+ ATPase) inhibitor with vasoconstrictive properties. The hemodynamic and humoral effects of a 2-hour intravenous saline infusion were studied in 25 borderline hypertensives characterized on the basis of their forearm venous distensibility (VV30) in normal ($n = 15$) and low ($n = 10$) VV30. VV30 was slightly reduced by saline in the entire hypertensive group (1.47 vs 1.36 ml/100 ml; $p < 0.05$), whereas blood pressure and plasma Na^+/K^+ ATPase inhibitor were unchanged. Normal VV30 showed a sudden increase in plasma Na^+/K^+ ATPase inhibitor in response to saline associated with an increase in blood pressure, a forearm arterial and venous constriction, and a sluggish suppression in plasma renin activity, whereas low VV30 exhibited a completely opposite pattern. The changes in plasma Na^+/K^+ ATPase inhibitor inversely correlated to VV30 decreases in borderline hypertensives with normal VV30 ($r = -0.49$; $p < 0.05$), whereas they did not in all hypertensive patients. Atrial natriuretic peptide response to saline infusion was delayed in normal VV30 and inversely related to the changes in Na^+/K^+ ATPase inhibitory activity ($r = -0.42$; $p < 0.05$) attained after 2 hours of infusion in the entire hypertensive population. Results of this study suggest the ability of acute volume expansion to reduce peripheral venous distensibility in borderline hypertensive patients. The extent of venoconstrictive response is related to the increase in plasma levels of an endogenous Na^+/K^+ ATPase inhibitor whose release is apparently promoted either by delayed atrial natriuretic peptide stimulation or sluggish suppression of plasma-renin activity.

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The role of capacitance vessel in the regulation of cardiac output and fluid volume has been widely demonstrated in animal¹ as well as in human^{2,3} studies. An early reduction in venous compliance has been reported in borderline hypertensives⁴ who also exhibited a redistribution in plasma volume from peripheral to cardiopulmonary circulation⁵ and an altered reflex suppression of plasma renin activity.^{6,7} Functionally, the decreased venous distensibility is thought to contribute to the increase in blood pressure observed in borderline hypertensives, which is partially prevented by short-term peripheral venodilatation.⁸ Beside these findings, several studies have supported the existence in human plasma of an endogenous sodium ion/potassium ion adenosine triphosphatase (Na^+/K^+ ATPase) inhibitor released as a physiologic response to compensate for excessive extracellular volume expansion^{9,10} and able to influence vascular tone and sodium handling.¹¹ The interest in altered Na^+/K^+ pump activity lies not so much in the activity itself, but more in the cellular consequences that alteration in such activity can have on vascular tone. Many investigators¹¹⁻¹³ have suggested that the blockade of vascular Na^+/K^+ ATPase activity would cause a progressive vasoconstriction accounting for the increase in peripheral vascular resistance associated with hypertension. However, despite these observations, very few data are available at present on the relation between venous tone and plasma humoral factors related to extracellular volume control. Because acute extracellular volume expansion can be easily achieved by intravenous saline infusion, the present study was performed in borderline hypertensive patients, first to investigate if this maneuver modifies individual venous distensibility and, second, if possible changes of venous distensibility are linked to the release of circulating factors influencing vascular tone.

METHODS

Twenty-five young borderline hypertensives (16 male and 9 female patients, aged 15 to 28 years [mean \pm standard deviation 23 ± 4]) were selected for the study. Patients were diagnosed to have borderline hypertension in agreement with criteria described elsewhere¹⁴ and all had normal plasma renin activity according to a standard nomogram relating upright plasma renin activity to 24-hour urinary sodium excretion. Briefly, we classified as borderline hypertensives those subjects who, on 3 different occasions, exhibited at least 1 recumbent casual diastolic blood pressure value $>$ and

TABLE I Baseline Characteristics of Borderline Hypertensive Patients

	All Pts. (n = 25)	Normal VV30 (n = 15)	Low VV30 (n = 10)
Systolic blood pressure (mm Hg)	133 ± 9	133 ± 5	133 ± 11
Diastolic blood pressure (mm Hg)	73 ± 6	70 ± 3	76 ± 8
Heart rate (beats/min)	72 ± 7	72 ± 8	71 ± 7
Forearm blood flow (ml/min/100 ml)	2.8 ± 0.5	3.0 ± 0.9	2.6 ± 0.8
Forearm vascular resistance (Units)	32.5 ± 8	29.8 ± 9	35.3 ± 9
VV30 (ml/100 ml)	1.4 ± 0.2	1.7 ± 0.2	1.1 ± 0.2*
Plasma renin activity (ng/ml/hour)	3.2 ± 1	2.9 ± 1	3.3 ± 1
Plasma aldosterone (pg/ml)	215 ± 112	199 ± 130	229 ± 107
Creatinine clearance (ml/min/1.73 m ²)	82 ± 15	80 ± 16	84 ± 14
Urinary dopamine (μg/g creatinine)	142 ± 62	138 ± 50	145 ± 63
Ouabain-sensitive ⁸⁶ Rb uptake (nmoles K ⁺ /hour/10 ⁸ cells)	9.4 ± 0.8	10.0 ± 0.4	8.8 ± 0.7†
Na ⁺ -K ⁺ ATPase inhibitory activity (%)	44 ± 14	38 ± 10	48 ± 10†
Atrial natriuretic peptide (pg/ml)	23 ± 11	20 ± 5	25 ± 15

* p < 0.005; † p < 0.01 normal vs low VV30.

ATP = adenosine triphosphatase; K⁺ = potassium ion; Na⁺ = sodium ion; VV30 = forearm venous distensibility.

1 < 90 mm Hg. Secondary hypertension was excluded by physical as well as laboratory examination and none of the patients had history or findings of heart or renal disease with serum creatinine ranging from 0.6 to 1.1 mg/dl. All patients were free of antihypertensive medication and they were maintained at a constant sodium intake of 100 mmol/day for the 7 days before the study. Borderline hypertensives were studied in a metabolic ward at a constant room temperature of 24°C and after

30 minutes of rest in the recumbent position. The study protocol was approved by the Ethical Committee of the University of Bologna and each patient gave informed consent.

Blood pressure and forearm hemodynamics: Systolic, diastolic, mean blood pressure and heart rate were recorded by an automatic device (Sentry Automated Screening Devices, Costa Mesa, California) and the values are reported as a mean of 5 consecutive measure-

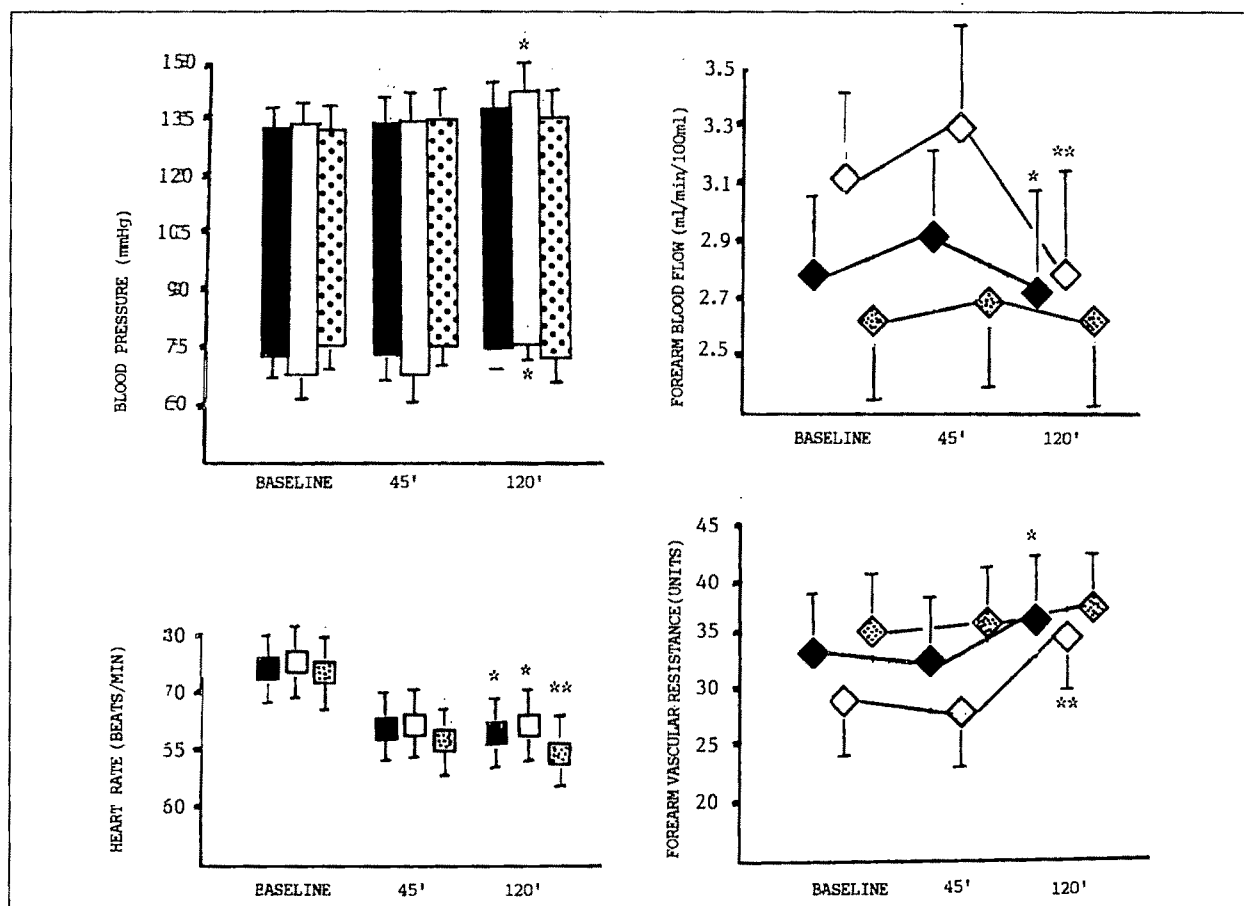


FIGURE 1. Changes in blood pressure, heart rate and forearm hemodynamics observed after 45 and 120 minutes of sodium chloride infusion in the overall population of borderline hypertensives (filled bars) and in the 2 subgroups with normal (open bars) and low (dotted bars) forearm venous distensibility. * p < 0.05; ** p < 0.005 compared with baseline.

ments. Forearm blood flow and vascular resistance and forearm venous distensibility were measured by venous occlusion plethysmography using a mercury-in-silastic strain gauge according to a standardized methodology previously described.^{6,7} Forearm venous distensibility at a congesting pressure of 30 mm Hg above the minimum occlusion pressure (VV30) was derived from the volume/pressure curve for each subject and expressed as ml/100 ml. Baseline VV30 values measured in borderline hypertensives were compared with those recorded in a group of age- and sex-matched normotensive controls without family history of hypertension. On the basis of these values, we classified as normal or low VV30 those borderline hypertensives whose VV30 fell respectively within or below the range found in normotensive controls.

Biochemical variables: Plasma renin activity and plasma aldosterone were measured by radioimmunoassay, plasma and urinary sodium and potassium by flame photometry, creatinine clearance and % fractional excretion of sodium were calculated by standard formulas, and urinary dopamine was measured by high pressure liquid chromatography using an electrochemical detector. Plasma levels of atrial natriuretic peptide (ANP) were determined by commercial radioimmunoassay (Amersham ANP Radio Immuno Assay System) after purification of plasma on Bond-Elut C18 disposable columns. The sensitivity of the assay allowed detection of 4 pg per assay tube. Plasma Na⁺/K⁺ ATPase inhibitory activity was measured following a procedure described elsewhere^{15,16} and expressed as % throughout the study. In addition, the baseline Na⁺-pump activity was assayed individually by measuring the red blood cells rubidium uptake (86Rb).

Protocol: A 24-hour urine collection for determination of sodium, potassium, dopamine and creatinine was obtained the day before sodium loading to ensure that subjects were in sodium balance before the beginning of the experimental procedure. The day of examination, after an overnight fasting and a complete voiding, the borderline hypertensives underwent a 2-hour saline infusion by way of a venous cannula inserted in an antero-cubital vein and placed 30 minutes before the infusion was begun. NaCl was infused at a rate of 0.4 ml/min/kg for the first 45 minutes and at 0.16 ml/min/kg for the following 75 minutes. Immediately before infusion, baseline blood and urine samples were obtained and the cardiopulmonary receptor sensitivity was tested individually by assessing the forearm vasodilator response to passive 60° leg-raising, a technique known to increase central venous pressure.¹⁷ Thereafter, baseline blood pressure and forearm hemodynamics were measured in recumbent position and the measurements were repeated after 45 and 120 minutes of saline infusion concomitantly with the blood sampling for measurement of biochemical variables. Urinary dopamine and creatinine were determined at the end of the NaCl loading, whereas postloading urinary sodium and potassium excretions were subdivided into 2 separate specimens defined, respectively: immediate (0 to 2 hours) and delayed (2 to 24 hours).

TABLE II Urinary Electrolyte Excretion After Salt Loading in Normal and Low Forearm Venous Distensibility (FVD)

	Normal FVD (n = 15)	Low FVD (n = 10)
0-2 hours	7.4 ± 0.1	6.8 ± 1
Na ⁺ urine (μmol/min/kg b.w.)		
2-24 hours	2.5 ± 0.5	3.3 ± 0.7
0-2 hours	1.8 ± 0.6	2.4 ± 0.3*
K ⁺ urine (μmol/min/kg b.w.)		
2-24 hours	0.54 ± 0.1	0.51 ± 0.1

* p < 0.05 normal vs low FVD.
K⁺ = potassium ion; Na⁺ = sodium ion; b.w. = bodyweight.

Statistical analysis: Results are expressed as mean ± standard deviation. Analysis of variance for repeated measurements was performed for multiple comparison of modifications in blood pressure, forearm hemodynamics, plasma levels of ANP and Na⁺/K⁺ ATPase inhibitor observed during NaCl loading. In the presence of significant values of "F," the least significant difference test was applied and p values > 0.05 were rejected. The paired *t* test was used to compare the intraindividual modifications of other normally distributed biochemical variables, whereas the unpaired *t* test was performed for comparison between the 2 groups of border

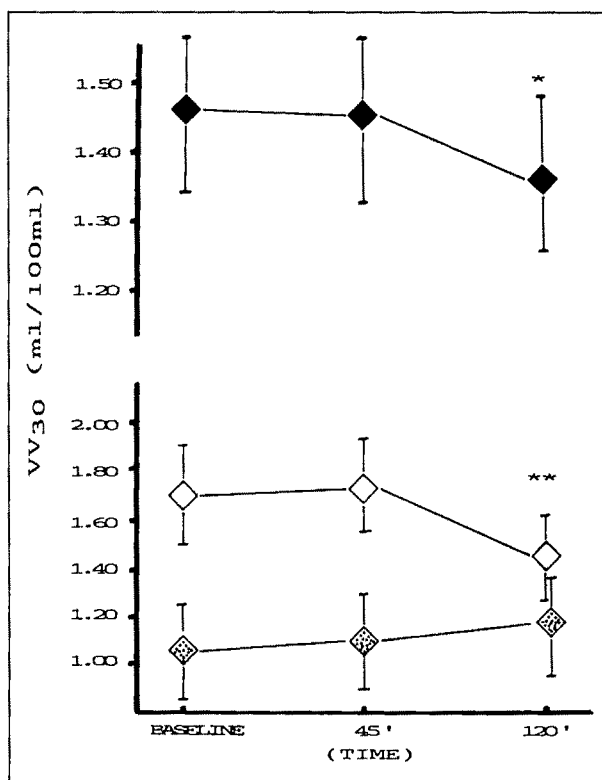


FIGURE 2. Changes in forearm venous distensibility (VV30) elicited by 45 and 120 minutes of sodium chloride loading in the overall population of borderline hypertensives (filled symbols) and in the 2 subgroups with normal (open symbols) and low (dotted symbols) forearm venous distensibility. * p < 0.05; ** p < 0.005 compared with baseline.

line hypertensives. Fisher's exact test or Wilcoxon signed rank sum test was performed to compare the nonhomogeneously distributed data. Linear regression analysis was performed by the least-squares method.

RESULTS

The baseline characteristics of the studied patients as well as those of the 2 subgroups, normal and low VV30, are summarized in Table I. Compared with normotensive controls 15 patients were classified as normal VV30 and 10 as low VV30. Aside from the expected difference in venous distensibility, the low VV30 group had increased levels of plasma Na^+/K^+ ATPase inhibitor, reduced ouabain-sensitive red blood cells 86Rb uptake and a slight, but not significant, tendency toward forearm vasoconstriction when compared with the normal VV30 group. The effects of NaCl loading on systemic and forearm arterial hemodynamics are shown in Figure 1. Blood pressure and heart rate did not change in the general population, but a slight increase was observed in forearm vascular resistance concomitantly

with a decrease in venous distensibility (Figure 2). This trend was enhanced in the normal VV30 group, who had an increase in blood pressure and a marked forearm arterial and venous constriction, whereas the low VV30 group showed a tendency toward a completely opposite pattern. During volume expansion, a generalized decrease in plasma renin activity (from 1.9 ± 1 to 1 ± 0.6 ng/ml/hour; $p < 0.005$) and plasma aldosterone (from 172 ± 70 to 63 ± 38 pg/ml; $p < 0.005$) occurred along with an increase in % fractional excretion of sodium (from 0.61 ± 0.3 to $1.16 \pm 0.3\%$; $p < 0.05$), urinary dopamine excretion (from 142 ± 62 to 299 ± 130 $\mu\text{g/g}$ creatinine; $p < 0.005$) and plasma ANP concentration (from 23 ± 11 to 36 ± 14 pg/ml; $p < 0.001$), whereas plasma Na^+/K^+ ATPase levels were apparently not affected by the procedure (from 44 ± 14 to $43 \pm 12\%$; difference not significant). In the 2 separate groups of borderline hypertensives, the humoral response to saline resulted in a blunted decrease in plasma renin activity and aldosterone in the normal VV30 group, who also had a greater increase in % fractional excretion of sodi-

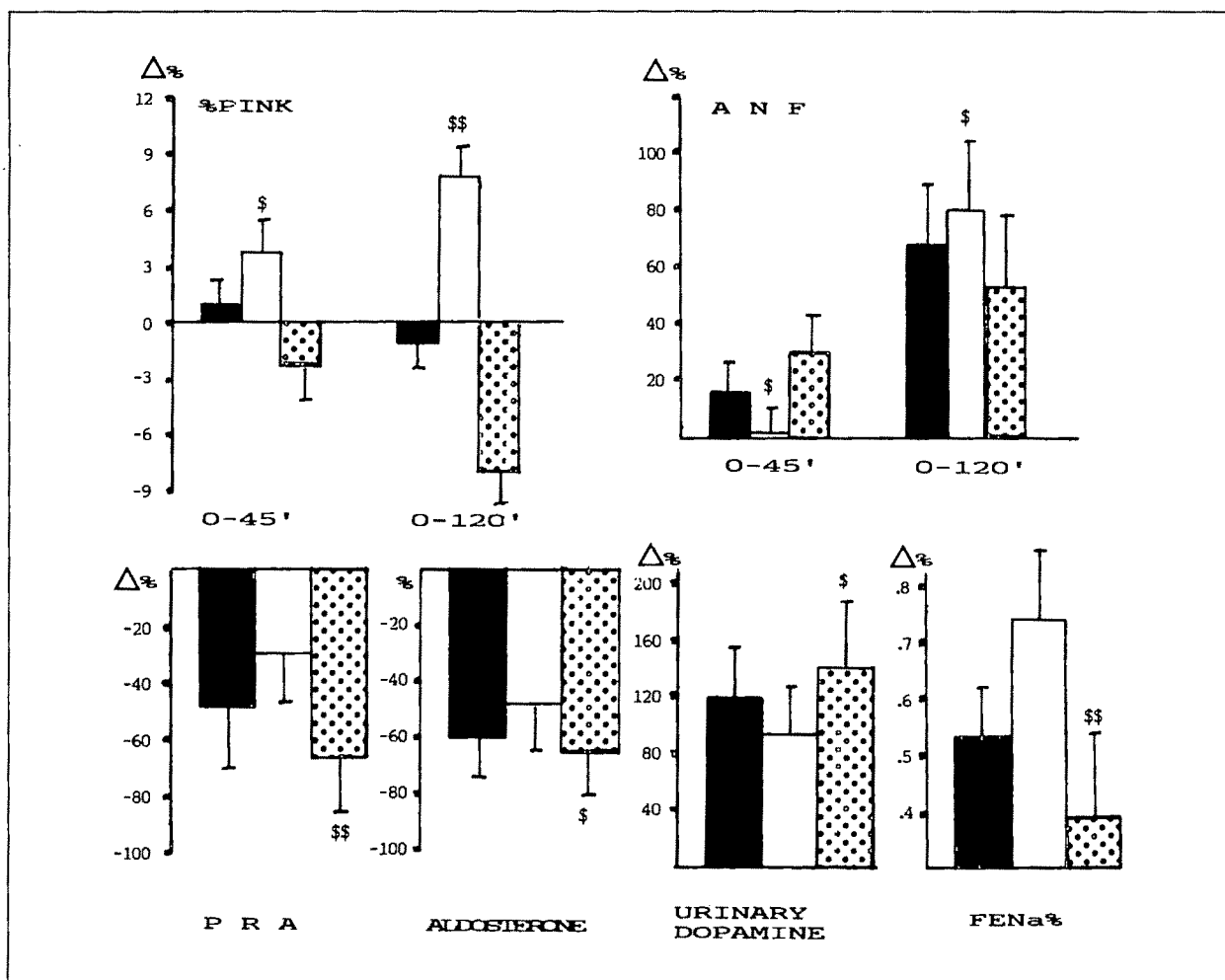


FIGURE 3. Percent changes of some humoral variables determined by saline infusion in the overall population of borderline hypertensives (filled bars) and in the 2 subgroups with normal (open bars) and low (dotted bars) forearm venous distensibility (FVD). ANF = atrial natriuretic factor; FENa% = excreted fraction of filtered sodium; PINK = plasma Na^+/K^+ ATPase inhibitor; PRA = plasma renin activity. \$ $p < 0.05$; \$\$ $p < 0.005$ normal compared with low FVD.

um (Figure 3). ANP levels increased in response to NaCl in both groups of borderline hypertensives, reaching the peak plasma level after 45 and 120 minutes, respectively, in low and normal VV30. A significant increase in plasma levels of Na^+/K^+ ATPase inhibitor, already evident after 45 minutes of saline infusion, was achieved only in those with normal VV30, whereas dopamine excretion was enhanced in the low VV30 group (Figure 3). We were unable to find any difference between immediate and delayed urinary sodium excretion, although the urinary sodium/potassium ratio calculated on the 0- to 2-hour urine specimen was higher in the normal VV30 (4.0 ± 1) than in the low VV30 (3.1 ± 1 ; $p < 0.005$) group as a result of lower potassium excretion (Table II). In the overall borderline hypertensive population, changes in plasma levels of Na^+/K^+ ATPase inhibitor seen in response to 2 hours of saline loading, were inversely related to the extent of ANP response ($r = -0.42$; $p < 0.05$), whereas no relation was found between the former variable and the changes in VV30 that were, conversely, significantly correlated to the increase in plasma Na^+/K^+ ATPase inhibitory activity ($r = -0.49$; $p < 0.05$) in the normal VV30 subgroup.

DISCUSSION

The results of the present study clearly confirm previous observations dealing with the existence of a reduced venous distensibility in a subset of patients with borderline hypertension.^{4,8} Our findings provide insight into the interrelation between changes in peripheral venous tone and the pattern of humoral response to saline infusion. In our experimental conditions, acute volume expansion elicited a significant reduction in venous distensibility, which is enhanced in borderline hypertensive patients with normal venous tone who also exhibit a greater pressor response, a sluggish plasma renin activity suppression and an increase in circulating levels of an endogenous Na^+/K^+ ATPase inhibitor. A similar hemodynamic and humoral pattern in response to saline has been previously reported in borderline as well as essential hypertensive patients,^{7,16,18} even though the plasma levels of Na^+/K^+ ATPase inhibitor in the study of Tuck et al¹⁸ were not measured and the study focused on the concomitant occurrence of enhanced pressor response and delayed suppression of plasma renin activity.

The following discussion will focus mainly on the venous response to saline infusion, with the aim of shedding some light on the mechanism(s) underlying the changes in venous distensibility observed in response to acute extracellular volume expansion. We speculate that the observed changes in venous distensibility elicited by NaCl loading are related to plasma levels of an Na^+/K^+ ATPase inhibitor whose trend follows exactly the time course of venoconstrictive response in both hypertensive groups (Figures 2 and 3). The initial increase in Na^+/K^+ ATPase inhibitory activity that we observed in normal VV30 after the rapid phase of saline infusion would cause a peripheral venoconstriction promoting a progressive central shifting of circulating volume, which

could provide an explanation for the further release of Na^+/K^+ ATPase inhibitor and the delayed peak of ANP response observed in this subgroup (Figure 3). This sluggish ANP response would contribute to the increase in Na^+/K^+ ATPase inhibitory activity observed after 45 minutes, according to the finding of an inverse relation between the release of ANP and that of Na^+/K^+ ATPase inhibitors (previously described both in vitro^{19,20} and in vivo experimental conditions²¹). By contrast, in the low VV30 group, the reduced initial venous distensibility is probably responsible for a sudden distribution of the amount of infused fluids toward the cardiopulmonary region; this distribution explains the prompt ANP release, the greater renal dopamine excretion and the rapid reflex suppression of plasma renin activity and aldosterone (Figure 3 and Table II) that counteracts the excess in extracellular fluid volume and accounts for the lack of Na^+/K^+ ATPase inhibitor release and venoconstrictive response. The present observations are consistent with the vasoconstrictive properties of endogenous sodium transport inhibitors that have previously been reported by many workers in arterial vessels^{13,22,23}; however, no data are available on the effects of such a compound on venous tone.

With regard to the mechanism(s) accounting for the vasoconstrictive action of Na^+/K^+ ATPase inhibitors, several hypotheses have been postulated for the arterial wall system, including either an increase in cytosolic free calcium¹² or an inhibition of norepinephrine reuptake by adrenergic nerve terminals.^{24,25} Freas et al²⁶ showed that ^3H norepinephrine uptake can be blocked in the canine isolated saphenous vein by a heat-stable, nonprotein plasma factor with some similarities to our sodium transport inhibitor. Therefore, a possibility exists that circulating Na^+/K^+ ATPase inhibitors act on venous tissue indirectly by interfering with the sympathetic nerve activity and catecholamine reuptake, thus leading to a venoconstriction. Whichever mechanism underlies the interaction between venous wall and Na^+/K^+ ATPase inhibitors, the enhanced venoconstrictive response to NaCl loading seen in normal VV30 appears to be facilitated by the greater baseline Na^+/K^+ ATPase activity found in this subgroup. This condition, which can be inferred from the higher ouabain-sensitive ^{86}Rb uptake of red blood cells and lower levels of sodium pump inhibition (Table I), might exaggerate the effects of vascular Na^+/K^+ ATPase blockade, even in the presence of low levels of a specific inhibitor, thus accounting for the observed rapid and progressive development of venous constriction. An enhanced vasoconstrictive response to ouabain has already been described in borderline hypertensives,²⁷ thus confirming the existence of an increased vascular sensitivity to Na^+/K^+ ATPase inhibitors in these patients.

This study raises intriguing possibilities that acute changes in venous tone in response to saline can be related to the release of an endogenous Na^+/K^+ ATPase inhibitor. Our observations also confirm the existence of a relation between baseline peripheral venous tone, renin-angiotensin-aldosterone suppression and the release

of an endogenous sodium pump inhibitor. We suggest that the venoconstrictive response attained by most of the borderline hypertensives after saline infusion could represent the early stage of the generalized vascular abnormalities described in the prehypertensive phases.

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Usefulness of Bucindolol in Congestive Heart Failure

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The sympathetic hyperactivity of congestive heart failure (CHF) may worsen cardiovascular function by down-regulation of myocardial β -receptors. For this reason, β blockade is proposed to be useful in CHF. Bucindolol is a new β blocker that has intrinsic nonadrenergically-mediated vasodilation and may be valuable in the treatment of CHF. To test this, 19 patients with CHF were randomized in a double-blind protocol to 3 months of treatment with bucindolol (n = 12) or placebo (n = 7). Significant improvement was seen in the bucindolol group using invasive and noninvasive tests; treadmill time increased from 445 to 530 seconds (p = 0.04), Minnesota Living With Heart Failure Questionnaire score improved from 61 to 40 (p = 0.0001), cardiac output increased from 4.0 to 4.7 (p = 0.02), and systemic vascular resistance decreased from 1,888 to 1,481 (p = 0.04). Also, peak exercise heart rate and pulmonary capillary wedge pressure decreased significantly with treatment. There were no changes in the placebo group. We conclude that bucindolol may be an effective treatment for CHF when administered chronically and that its non-adrenergic vasodilation may be an important feature.

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The heightened sympathetic tone of chronic congestive heart failure (CHF) compromises myocardial function by down-regulating β_1 receptors and impairing response to exogenous catecholamines.¹ It has, therefore, been proposed that pharmacologic β blockade is actually useful in the treatment of chronic CHF.² Metoprolol has been most widely used for this purpose, but newer agents, with different properties, are being evaluated.³ Bucindolol is a member of a new class of β blockers that possesses peripheral vasodilating activity.⁴ Although bucindolol is reported to have mild intrinsic sympathomimetic activity in animals, its vasodilating effect is a direct one and is not due to intrinsic sympathomimetic activity *in vivo*.^{5,6} Because vasodilation is beneficial in CHF, a β blocker with vasodilation may be especially valuable.^{7,8} We evaluated bucindolol's usefulness in CHF in a randomized, double-blind trial of 19 patients.

METHODS

Patients: Patients in this study were referred to the University of Virginia for evaluation and treatment of CHF. Patients with stable, symptomatic CHF with a dilated cardiomyopathy due to either ischemic or idiopathic causes were selected if they met the following criteria: ejection fraction <40%; ability to perform treadmill exercise for ≥ 4 minutes, but not >16 minutes, on a modified Naughton protocol; no concurrent β -blocker use; no pulmonary contraindication to β blockade; and no concurrent severe illness. Twenty-one patients were enrolled between January and December 1988. One patient died during the prerandomization evaluation and 1 patient randomized to bucindolol was lost to follow-up. Thus, 19 patients completed the trial. Patients received diuretics, digoxin and afterload reduction as deemed appropriate by their primary physician.

There were 4 women and 15 men and the mean age was 54 years. Seven patients had an ischemic cardiomyopathy and 12 had an idiopathic dilated cardiomyopathy. Patients were classified as ischemic or idiopathic on the basis of available clinical information, such as recent catheterization, previous myocardial infarction or exercise thallium imaging. No patient's exercise capacity was limited by angina pectoris and no patient had roentgenographic pulmonary edema at study entry. One in each group had pleural effusions.

Study design: Prerandomization evaluation consisted of a history, physical examination, 2 treadmill tests (1 day apart), rest radionuclide ventriculography and pulmonary artery catheterization. Patients were then

TABLE I Baseline Characteristics

	Placebo (n = 7)	Bucindolol (n = 12)	p Value
Mean age	50	56	NS
No. men	6	9	NS
No. women	1	3	NS
No. taking digitalis	5	10	NS
No. taking vasodilator	7	8	NS
Ejection fraction	25	19	NS
NYHA II	1	0	NS
NYHA III	4	10	NS
NYHA IV	2	2	NS
No. idiopathic	5	7	NS
No. ischemic	2	5	NS

NYHA = New York Heart Association functional class; NS = not significant.

admitted to the hospital, given 2 to 3 test doses of open-label bucindolol, 12.5 mg orally 12 hours apart and observed for clinical compromise. All patients tolerated this dose and were randomized in a double-blind fashion in a 3:2 ratio to bucindolol or placebo, respectively, at a dose of 12.5 mg orally twice daily. Patients returned weekly for clinical evaluation and dosage was increased to 25 mg twice daily, 50 mg twice daily and finally 100 mg twice daily. All patients tolerated the maximum dose. They were continued on 100 mg twice daily for 8 more weeks (3 months from randomization) and then underwent the same battery of tests as the prerandomization evaluation. The only exception was the treadmill, where only 1 test was performed at 3 months.

This study was reviewed and approved by the University of Virginia Health Sciences Center Human Investigation Committee. It was funded by Bristol-Myers Laboratories, who also supplied the bucindolol or placebo tablets. All data were collected and analyzed by the authors.

Treadmill testing: Patients were exercised on a Quinton status 1000 treadmill, using a modified Naughton protocol and 2-minute stages. The test was limited by symptoms or upon completion of all stages. No test was terminated due to hypotension, arrhythmias or chest pain. Baseline exercise duration was taken from the second test performed during the baseline examination.

Radionuclide angiography: Patients were injected first with pyrophosphate and then 20 μ Ci of technetium. Transit time was measured by the first-pass technique, and ejection fraction by computer calculation of scintigraphic counts obtained by multiple-gated angiography performed in the 45° left anterior oblique "best septal" view.

Six-minute walk: Patients were instructed to walk back and forth along a measured corridor at their own pace, according to a previously described protocol.⁹ Additional encouragement was not given. The distance traveled in 6 minutes of walking was measured in feet.

Living With Heart Failure Questionnaire: The Minnesota Living With Heart Failure Questionnaire is a self-administered questionnaire copyrighted by the University of Minnesota that assesses the patient's ability to function in everyday life. Twenty-three questions, such as "Did your heart failure prevent you from living as wanted during the last month by making your working around the house or yard difficult?", are answered by the patient on a scale of 0 ("no") to 5 ("yes"); higher scores reflect greater impairment.

Hemodynamic measurements: One patient in each group was unable to undergo Swan-Ganz catheterization at 3 months and their hemodynamic data are excluded from analysis. Complete hemodynamic measurements were available in the remaining 6 placebo patients. Of the 11 bucindolol patients undergoing repeat

TABLE II Bucindolol—Paired Comparison

	No. of Patients	Baseline		3 Months		p Value
		Mean	(\pm SD)	Mean	(\pm SD)	
Noninvasive data						
Treadmill time (s)	12	445	142	530	218	0.04
6-minute walk (feet)	12	1,254	252	1,405	248	0.04
LHFQ score	12	51	18	40	24	0.0001
EF (%)	12	19	7	23	8	0.04
Transit time(s)	12	18.3	6.6	13.7	5.2	0.02
Rest data						
HR (beats/min)	11	90	21	82	12	NS
Mean BP (mm Hg)	11	96	12	94	15.3	NS
Pulmonary capillary wedge pressure (mm Hg)	11	27	9	20	9	NS
Cardiac output (liters/min)	11	4.0	1.2	4.7	0.9	0.02
Systemic vascular resistance (dynes cm^{-5})	8	1,888	524	1,481	162	0.04
Exercise data						
HR (beats/min)	11	127	24	96	18	0.0001
Pulmonary capillary wedge pressure (mm Hg)	10	42	15	28	12	0.04
Mean BP (mm Hg)	11	109	18	101	15	NS
Cardiac output (liters/min)	11	5.7	2.1	5.4	1.6	NS

BP = blood pressure; EF = ejection fraction; HR = heart rate; LHFQ = Minnesota Living With Heart Failure Questionnaire; NS = not significant; SD = standard deviation.

TABLE III Placebo—Paired Comparison

	No. of Patients	Baseline		3 Months		p Value
		Mean	(±SD)	Mean	(±SD)	
Noninvasive data						
Treadmill time (s)	7	496	205	506	234	NS
6-minute walk (feet)	6	1,132	392	1,117	345	NS
LHFQ score	5	53	30	47	23	NS
EF (%)	7	25	8	29	10	NS
Transit time (s)	7	13.9	3.4	13.1	3.2	NS
Rest data						
HR (beats/min)	6	90	12	83	11	NS
Mean BP (mm Hg)	6	89	8	93	9	NS
Pulmonary capillary wedge pressure (mm Hg)	6	23	11	23	14	NS
Cardiac output (liters/min)	6	5.3	1	4.9	0.8	NS
Systemic vascular resistance (dynes s/cm ⁻⁵)	6	1,260	239	1,368	213	NS
Exercise data						
HR (beats/min)	6	118	10	117	19	NS
Pulmonary capillary wedge pressure (mm Hg)	6	33	11	32	12	NS
Mean BP (mm Hg)	6	99	11	102	12	NS
Cardiac output (liters/min)	6	8.4	2.7	8.3	2.8	NS
Abbreviations as in Table II.						

Abbreviations as in Table II.

Swan-Ganz catheterization, only 10 had baseline and 3-month peak exercise pulmonary capillary wedge pressure measurements and 8 had data to calculate systemic vascular resistance at both times.

After overnight fasting, patients had a 7Fr Swan-Ganz catheter placed from either the brachial or jugular vein. Patients were positioned onto a bicycle ergometer while remaining in the supine position. The catheter was advanced to the pulmonary artery using fluoroscopic guidance. Right atrial, ventricular, pulmonary artery and balloon wedge pressures were recorded on an Electronics for Medicine strip recorder. Cardiac output was determined by computer calculation of thermodilution curves after the injection of 10 cc of a chilled dextrose solution. Three measurements were obtained. Brachial artery blood pressure was measured with an automated blood pressure cuff.

Patients then exercised, recumbent upon the bicycle ergometer, until limited by symptoms, according to a stepwise protocol: 25 watts, 50 watts, 75 watts and up to 100 watts in 3-minute stages. Cardiac output, pulmonary capillary wedge pressure and brachial artery pressure were again measured at peak exercise. Right atrial pressure was not repeated and so systemic vascular resistance was not calculated at peak exercise.

Systemic vascular resistance and mean blood pressure were calculated in the usual way.

Statistical analysis: Bucindolol and placebo patients were compared at baseline with respect to gender, etiology of CHF, use of digitalis and use of vasodilators with a Fisher exact test. New York Heart Association functional class was compared with a nonparametric test (Mann-Whitney) and ejection fraction and age were compared with an unpaired *t* test.

Bucindolol's efficacy was analyzed in 2 ways. First, bucindolol-treated patients served as their own control

subjects in a comparison of baseline and 3-month values using a paired *t* test. Then, changes were compared between placebo and bucindolol-treated patients using an unpaired *t* test after normalizing data to baseline values. All tests were 2-tailed and probability values <0.05 were considered significant. Calculations were performed using a VAX 8200 computer (Digital Equipment Corporation, Marlboro, Massachusetts) and RS-1 software (BBN Software Products Corporation, Cambridge, Massachusetts).

RESULTS

Baseline comparison: Bucindolol and placebo groups were similar with respect to age, gender, digitalis use, vasodilator use, New York Heart Association functional class and etiology of CHF (Table I). The mean ejection fraction of the placebo group was slightly higher than the bucindolol group, but this did not reach statistical significance. Rest cardiac output and peak exercise cardiac output were significantly lower and systemic vascular resistance higher in the bucindolol group compared to the placebo group ($p < 0.05$).

Paired analysis—noninvasive data: The mean values of all noninvasive parameters in the bucindolol group showed statistical improvement between the baseline and 3-month examinations (Table II). Improved exercise capacity was seen as increased treadmill time and as distance walked in 6 minutes. This was paralleled by improved daily function as shown by lower scores in the Living With Heart Failure Questionnaire. Radionuclide parameters also showed improved cardiovascular function; ejection fraction increased slightly and transit time decreased.

Paired analysis—rest hemodynamic data: Although average resting heart rate decreased slightly with treatment, the difference did not attain statistical

significance (Table II). There was no significant change in mean blood pressure or pulmonary capillary wedge pressure. Both resting cardiac output and systemic vascular resistance improved.

Paired analysis—exercise hemodynamics: Unlike the rest data, there was a significant attenuation of peak exercise heart rate and pulmonary capillary wedge pressure with 3 months of bucindolol treatment (Table II). Neither mean blood pressure nor cardiac output at peak exercise changed significantly. There was no difference in bicycle work performed at 3 months compared to prerandomization.

Paired analysis—placebo: A paired comparison of all noninvasive and hemodynamic parameters was also done for placebo-treated patients and there were no significant changes (Table III).

Unpaired analysis—bucindolol vs placebo: When the bucindolol and placebo groups were compared by percent change, no significant difference could be found for any noninvasive test. There were significant differences among hemodynamic variables (Figure 1). At rest, cardiac output improved in the bucindolol group but decreased in the placebo group ($p = 0.02$). Systemic vascular resistance decreased in the bucindolol group and did not change in the placebo group ($p = 0.02$). Peak exercise heart rate decreased more in the bucindolol group than in the placebo group ($p = 0.0003$). The other hemodynamic variables did not differ significantly in their changes.

Medication changes: Furosemide dosage was changed during the study in 5 patients. One placebo patient's dose was increased from 80 mg daily to 200 mg daily and 3 bucindolol patients had their daily dose increased from 20 to 40, 120 to 240, and 40 to 80 mg, respectively. Another bucindolol patient's dose of furosemide was decreased from 240 to 160 mg daily. Captopril dose was doubled in 1 placebo patient, from 12.5 mg 3 times a day to 25 mg 3 times a day and halved in 1 bucindolol patient from 25 mg 3 times a day to 12.5 mg 3 times a day.

DISCUSSION

Our data show that patients improved with 3 months of bucindolol therapy when compared to their own baseline, but placebo patients did not. These findings agree with other published work using bucindolol. The mechanism of improvement may be due to greater contractility, afterload reduction or both.

Results of this placebo-controlled, double-blinded study trial are internally consistent; bucindolol-treated patients showed a modest, but statistically significant improvement in all parameters. Resting cardiovascular status changed favorably as shown by radionuclide and hemodynamic measurements. Exercise capacity measured by treadmill time and by distance walked in 6 minutes improved with treatment and this was reflected in daily life as lower Living With Heart Failure Questionnaire scores with treatment. This improved exercise capacity is likely due to improved cardiovascular function as evidenced by a lower pulmonary capillary wedge pressure at peak exercise. We believe that the improved function seen in the bucindolol group cannot be wholly ascribed to a placebo effect. These data, taken collectively, indicate that bucindolol improves CHF when administered chronically.

Our results are in agreement with those of Gilbert et al,¹⁰ who have reported on a similar trial of bucindolol in dilated cardiomyopathy. They, too, found significant improvements in cardiac index, ejection fraction and hemodynamics. They did not, however, show improvement in exercise capacity and used a lower average dosage of bucindolol.

The fall in systemic vascular resistance with bucindolol may be due to its direct vasodilating effect or may be an epiphenomenon. Perhaps β blockade provides the sole means of improvement, and the decrease in systemic vascular resistance is a secondary event that is not due to a direct drug effect. We think this is unlikely since the vasodilating action of bucindolol has been documented in animal and human experiments.^{5,6} Additionally, if β blockade were the sole mechanism of im-

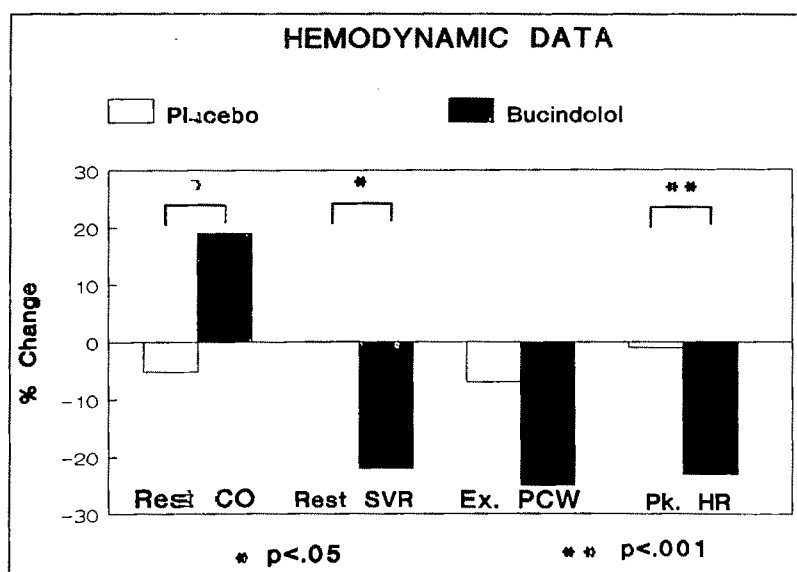


FIGURE 1. Bar graph of hemodynamic data. CO = cardiac output; SVR = systemic vascular resistance; Ex. PCW = exercise pulmonary capillary wedge pressure; Pk. HR = peak heart rate.

provement, then a decrease in systemic vascular resistance should occur with the use of other β blocking agents. Both propranolol and pindolol, however, have been found to increase systemic vascular resistance,¹¹ although 1 study using metoprolol found systemic vascular resistance to decrease with treatment.¹²

A significant decrease in resting heart rate could not be shown in this study, but the attenuation of peak exercise heart rate was marked. This response is mirrored by changes in pulmonary capillary wedge pressure. Rest pulmonary capillary wedge pressure did not significantly improve but peak exercise pulmonary capillary wedge pressure decreased markedly. Peak exercise cardiac output and work achieved during bicycle ergometry did not change at 3 months compared to prerandomization, indicating that bucindolol's favorable effect on exercise pulmonary capillary wedge pressure cannot be attributed to less cardiovascular stress at 3 months. Diminution of peak exercise heart rate is reported with other β blockers (metoprolol and pindolol), but attenuation of pulmonary capillary wedge pressure is not.^{13,14} This suggests that bucindolol's effect on exercise wedge pressure is not due to lowering peak heart rate alone, since all β blockers decrease exercise heart rate. Improved systolic function or afterload reduction may explain bucindolol's effect on exercise hemodynamics.

Study limitations: By study design, more patients were randomized to the treatment group than the placebo group. This was done in an effort to increase the possibility of detecting any adverse reactions to bucindolol. There were none. The small number of patients in the placebo group, along with the natural variability among patients, makes comparisons using the placebo group difficult. This is not a major shortcoming since the paired analysis of bucindolol-treated patients showed significant improvement in all parameters, including the noninvasive tests. A larger study is needed to evaluate further differences between treatment effects of bucindolol and placebo.

This protocol used 2 baseline treadmill tests. A more pure, albeit burdensome, methodology is to administer serial exercise tests until each patient consistently performs the same work between tests. This limitation,

however, does not invalidate our conclusion because bucindolol patients were found to improve with all other measures of cardiovascular function.

We emphasize that bucindolol was started at a low dose and slowly increased. More rapid titration may cause hemodynamic embarrassment. Furthermore, some patients may require adjustment of other medications after bucindolol's initiation.

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Failure of Captopril to Prevent Nitrate Tolerance in Congestive Heart Failure Secondary to Coronary Artery Disease

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The possible role of angiotensin-converting enzyme inhibition in preventing or minimizing tolerance to intravenous nitroglycerin in severe congestive heart failure (CHF) was studied by quantitating the degree of tolerance in 12 patients receiving nitroglycerin (group 1) and in 9 patients (group 2) receiving nitroglycerin and concurrent treatment with captopril (60 ± 29 mg/day). At peak effect, nitroglycerin produced almost identical hemodynamic changes in both groups, with significant decreases in right atrial and pulmonary arterial wedge pressure, systolic blood pressure and systemic and pulmonary vascular resistances. Cardiac index increased.

The extent of nitrate tolerance was calculated for each hemodynamic parameter as the percentage loss of the peak effect achieved by the drug. At 24 hours, $98 \pm 80\%$ of the benefit achieved with respect to right atrial pressure was lost in group 1 and $61 \pm 74\%$ in group 2 (group 1 vs 2, difference not significant). For pulmonary arterial wedge pressure, $51 \pm 31\%$ (group 1) and $85 \pm 53\%$ (group 2) (difference not significant) of the effect was lost, and for cardiac index, $53 \pm 58\%$ (group 1) and $54 \pm 44\%$ (group 2) (difference not significant). Tolerance was also almost identical regarding systolic blood pressure and systemic and pulmonary vascular resistance. Thus, the extent of tolerance to high-dose intravenous nitroglycerin in CHF was unaltered by administration of captopril, indicating that in clinical dosage, counter-regulatory neurohumoral mechanisms involving the renin-angiotensin system appear to be unimportant in its development.

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The beneficial effect of nitrate therapy in patients with congestive heart failure (CHF) may be rapidly offset by the development of tolerance to the drug within 24 to 48 hours.¹⁻⁴ Two primary mechanisms have been proposed⁴⁻⁶: (1) a cellular mechanism, in which depletion of sulfhydryl groups or alteration of the guanylate cyclase pathway is followed by attenuation of the effect of nitrates,^{5,7-10} and (2) a systemic mechanism, in which hemodynamic changes produced by nitroglycerin trigger a counter-regulatory neurohumoral response,^{11,12} with stimulation of the renin-angiotensin pathway, fluid retention and a secondary deterioration in hemodynamics. In keeping with the cellular mechanism is the evidence that administration of the sulfhydryl donor N-acetyl cysteine may ameliorate nitrate tolerance,^{4,13} while in keeping with the neurohumoral mechanism is the increase in plasma renin activity and body weight that has been observed during nitrate administration⁴ and the rebound vasoconstrictive changes that occur in some patients on withdrawal of nitrate therapy.¹¹ The present study examined in more detail the role of the renin-angiotensin pathway in the development of nitrate tolerance. We quantitated the extent of tolerance to intravenous nitrates in patients with CHF, and compared the data with those of patients concurrently receiving the angiotensin-converting enzyme inhibitor captopril.

METHODS

Study patients: The study involved 21 patients (18 men, 3 women) with severe (New York Heart Association functional class IV) CHF in sinus rhythm, who required hemodynamic monitoring as part of their clinical management. Their age ranged from 38 to 78 years. The etiology of CHF was advanced coronary artery disease with extensive regional and global left ventricular dysfunction. In all, the pulmonary arterial wedge pressure was ≥ 16 mm Hg and systolic blood pressure ≥ 90 mm Hg. Long-acting nitrate and other vasodilator therapy was discontinued at least 48 hours before the study. Baseline drug therapy with digoxin (10 patients) and furosemide (21 patients, dose 40 to 160 mg/day) was continued at a constant dosage schedule throughout the study period. Diuretic was administered at the same time each day, 6 hours after commencement of the nitroglycerin infusion.

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TABLE I Peak Hemodynamic Effect of Nitroglycerin

	RAP mm Hg		PCWP mm Hg		CI liters/min/m ²		SBP mm Hg		SVR dyne · s · cm ⁻⁵		PVR dyne · s · cm ⁻⁵		HR min ⁻¹	
	C	N	C	N	C	N	C	N	C	N	C	N	C	N
Group 1														
1	3	0	25	5	2.3	3.2	129	116	1,768	1,200	295	139	74	100
2	22	1	30	9	2.2	3.3	124	105	2,225	1,697	655	178	94	94
3	6	1	20	11	2.0	2.0	167	143	2,116	1,652	—	—	46	47
4	13	6	28	19	1.4	2.2	152	118	2,052	1,124	730	432	60	60
5	11	3	27	15	2.6	3.1	118	99	880	693	256	160	97	92
6	2	0	32	14	2.9	2.9	102	88	1,710	1,303	166	69	90	78
7	—	—	28	16	1.9	3.2	127	104	—	—	147	75	95	105
8	8	5	34	16	2.0	3.1	127	110	1,640	865	287	84	92	95
9	3	0	29	11	2.6	3.1	171	155	1,800	1,350	300	280	86	88
10	6	2	34	13	2.2	2.7	170	144	2,067	1,600	289	229	68	74
11	3	1	18	7	1.8	2.7	113	107	1,848	1,143	303	114	90	107
12	4	1	18	8	1.7	2.6	100	98	1,625	1,040	100	87	88	93
Mean	7	2	27	12	2.1	2.8	133	116	1,794	1,242	321	168	82	86
SD	6	2	6	4	0.4	0.4	25	21	364	320	197	110	16	18
P value	0.007		<0.001		0.0001		<0.0001		<0.0001		0.004		NS	
Group 2														
1	3	1	23	9	1.9	3.3	157	150	2,194	904	320	93	60	74
2	10	3	39	15	2.5	3.3	139	117	1,404	860	245	112	97	126
3	15	7	27	15	2.0	2.6	102	84	1,417	907	206	124	71	85
4	11	8	22	12	3.1	3.1	125	100	929	828	116	106	102	93
5	14	5	31	24	1.3	2.5	175	130	3,789	1,675	674	232	77	103
6	15	3	35	15	1.7	2.1	107	106	1,677	1,400	232	232	83	83
7	12	1	31	17	2.4	3.0	114	100	1,460	992	120	120	110	110
8	10	7	17	13	2.3	2.7	110	105	964	845	436	329	88	103
9	3	0	25	15	2.8	3.4	108	80	1,035	724	157	76	79	79
Mean	10	4	28	15	2.2	2.9	126	103	1,652	1,008	278	158	85	95
SD	5	3	6	4	0.5	0.4	25	16	893	317	179	86	16	16
P value	0.001		<0.001		0.001		0.005		<0.02		0.03		0.05	
Group 1 vs group 2														
P value	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
C = control; CI = cardiac index; HR = heart rate; N = nitroglycerin (peak effect); NS = not significant; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SEP = systolic blood pressure; SD = standard deviation; SVR = systemic vascular resistance.														

C = control; CI = cardiac index; HR = heart rate; N = nitroglycerin (peak effect); NS = not significant; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SBP = systolic blood pressure; SD = standard deviation; SVR = systemic vascular resistance.

The patients were randomly assigned to 2 treatment groups: group 1 (12 patients), who received nitroglycerin without captopril, and group 2 (9 patients), who received oral captopril (dose 25 to 100 mg, mean 60 ± 29 mg/day) during and for at least 24 hours before the onset of the study. Captopril was administered in the highest possible dose tolerated by the patient without dizziness or decrease in blood pressure to <90 mm Hg.

Data acquisition: A flow-directed catheter was positioned in the pulmonary artery and an arterial line in the radial artery 12 to 18 hours before measurements were made. Pressures were measured in the right atrium, pulmonary arterial and wedge position and radial artery. In the absence of mitral stenosis, the pulmonary arterial wedge pressure represents left ventricular end-diastolic pressure. Cardiac output and stroke volume were measured by thermodilution in triplicate at each stage of the study protocol. When a measurement deviated by more than 10% from the other 2 values, this value was discarded and an additional determination made. Body weight was recorded at the same time of day at the beginning and end of the study period. Blood samples for measurement of plasma renin activity and aldosterone were taken with the patient supine after 20 minutes supine bedrest.

Administration of nitroglycerin: After control hemodynamic measurements, nitroglycerin was administered by continuous intravenous infusion, increasing the dose rapidly over a period of 60 to 90 minutes until (1) the pulmonary arterial wedge pressure decreased to ≤ 10 mm Hg, or (2) systolic blood pressure decreased to ≤ 90 mm Hg or (3) there was an untoward clinical reaction (this did not occur). The dose of nitroglycerin (465 ± 481 , range 60 to 1,600 $\mu\text{g}/\text{min}$ in group 1; 413 ± 132 , range 240 to 660 $\mu\text{g}/\text{min}$ in group 2, difference not significant) was continued unchanged throughout the study period. Hemodynamic measurements were repeated 3, 6, 12 and 24 hours after the onset of infusion of nitroglycerin.

Quantitation of nitrate tolerance: The extent of nitrate tolerance was calculated separately for each hemodynamic parameter, as the percentage loss of the maximum effect achieved by nitroglycerin, e.g., for the extent of tolerance with regard to right atrial pressure, tolerance (%) = (measured right atrial pressure - minimal right atrial pressure) $\times 100$ / (control right atrial pressure - minimal right atrial pressure).

Statistical analysis: The effect of nitroglycerin at the time of each measurement and the extent of nitrate tolerance in patients receiving and those not receiving

captopril was examined using a 2-sample Student *t* test. A paired *t* test examined the changes in hemodynamic and neurohumoral measurements before and after 24 hours of nitroglycerin in each group.

RESULTS

Hemodynamic measurements and effect of nitroglycerin: Control hemodynamic measurements were similar in patients receiving and those not receiving captopril, and improved significantly and almost identically after nitroglycerin (Table I, Figures 1 to 6). At peak effect, right atrial pressure decreased by $77 \pm 21\%$ in group 1 and $65 \pm 25\%$ in group 2 (group 1 vs 2, difference not significant), and pulmonary arterial wedge pressure by $55 \pm 13\%$ and $45 \pm 14\%$ (difference not significant). Cardiac index increased by $36 \pm 23\%$ and $35 \pm 29\%$ (difference not significant). The decreases in systemic (group 1, $31 \pm 10\%$; group 2, $33 \pm 18\%$; difference not significant) and pulmonary (group 1, $44 \pm$

23% , group 2, $35 \pm 27\%$, difference not significant) vascular resistances were similar in both groups. Systolic blood pressure decreased by $13 \pm 6\%$ in group 1 and $15 \pm 9\%$ in group 2 (group 1 vs 2, difference not significant).

Incidence and extent of nitrate tolerance: Nitrate tolerance developed in a third to two-thirds of patients in each group, with considerable individual variation. Defining tolerance as a loss at 24 hours of 50% or more of the benefit achieved by the drug, tolerance was observed with respect to right atrial pressure in 8 of 12 (67%) patients in group 1 and in 4 of 9 (44%) in group 2 (difference not significant). With respect to the wedge pressure, tolerance occurred in 6 of 12 (50%) patients in group 1 and in 6 of 9 (67%) in group 2 (difference not significant), while in the remainder there was continued efficacy of the drug at this time.

The extent of nitrate tolerance in both patient groups is shown in Figures 1 to 6. On the average, at 24

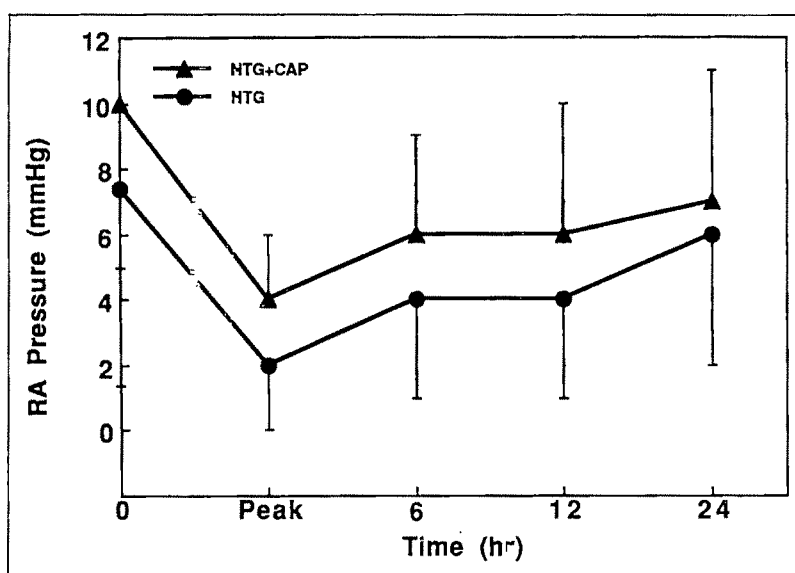


FIGURE 1. Right atrial (RA) pressure during administration of nitroglycerin in patients receiving (NTG + CAP) and those not (NTG) receiving captopril. There was no difference between the 2 patient groups.

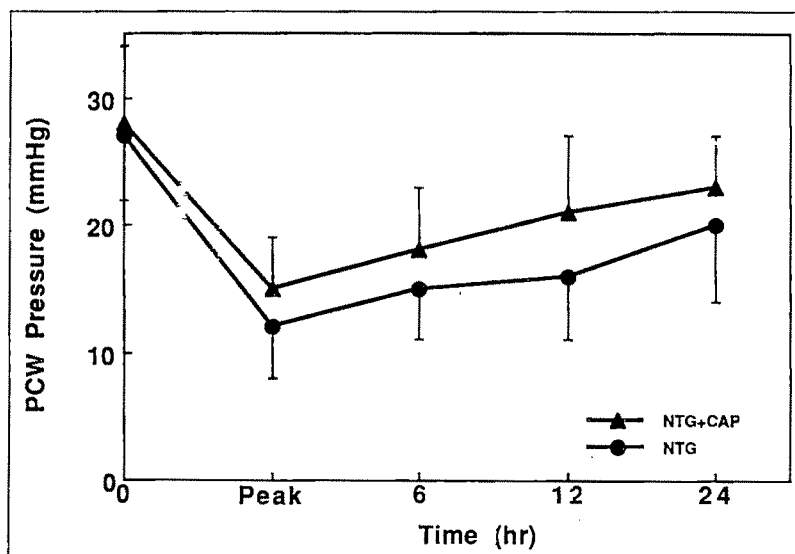


FIGURE 2. Pulmonary capillary wedge (PCW) pressure during administration of nitroglycerin in patients receiving (NTG + CAP) and those not (NTG) receiving captopril. There was no difference between the 2 patient groups.

hours, $98 \pm 80\%$ of the decrease in right atrial pressure had been lost in group 1 and $61 \pm 74\%$ in group 2 (group 1 vs 2, difference not significant), while the extent of tolerance for pulmonary vascular resistance was $160 \pm 305\%$ in group 1 and $167 \pm 296\%$ in group 2 (difference not significant). For cardiac index $53 \pm 58\%$ of the increase was lost in group 1 and $54 \pm 44\%$ in group 2 (difference not significant), while percentage tolerance regarding pulmonary arterial wedge pressure was $51 \pm 31\%$ in group 1 and $85 \pm 53\%$ in group 2 (difference not significant).

Plasma-renin activity, aldosterone and body weight: Plasma-renin activity was increased in a third of the patients in group 1 and in two-thirds of those in group 2, and was essentially unchanged after 24 hours of nitroglycerin (Table II). Aldosterone was also increased in both groups. In patients receiving captopril (group 2), the ratio of renin to aldosterone was markedly higher. There was marked individual variation in

both renin (range 0.4 to 95.0 ng of angiotensin I/ml/hour) and aldosterone (range 2 to 108 ng/dl) both before and after nitroglycerin. Body weight was unaltered in both groups after 24 hours of nitroglycerin.

DISCUSSION

Neurohumoral mechanisms in congestive heart failure and the effect of nitroglycerin: In CHF, there is a parallel and significant increase in plasma catecholamines, atrial natriuretic peptide¹⁴ and renin-aldosterone.¹⁵ Plasma renin activity may be increased to 10 times normal and plasma norepinephrine to more than 6 times normal in untreated patients.¹⁶ The plasma renin level shows considerable individual variability and is influenced by diuretic therapy.¹⁷ A high plasma renin level signifies an adverse prognosis, as does an increase in catecholamines and atrial natriuretic peptide.¹⁸ Angiotensin inhibitors may improve organ function¹⁹ and patient survival.²⁰

FIGURE 3. Cardiac index during administration of nitroglycerin in patients receiving (NTG + CAP) and those not (NTG) receiving captopril. There was no difference between the 2 patient groups.

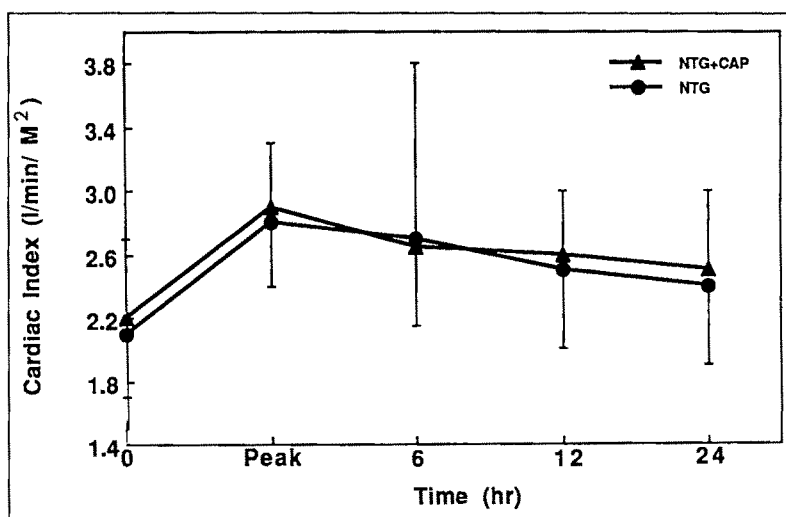


FIGURE 4. Systolic arterial pressure during administration of nitroglycerin in patients receiving (NTG + CAP) and those not (NTG) receiving captopril. There was no difference between the 2 patient groups.

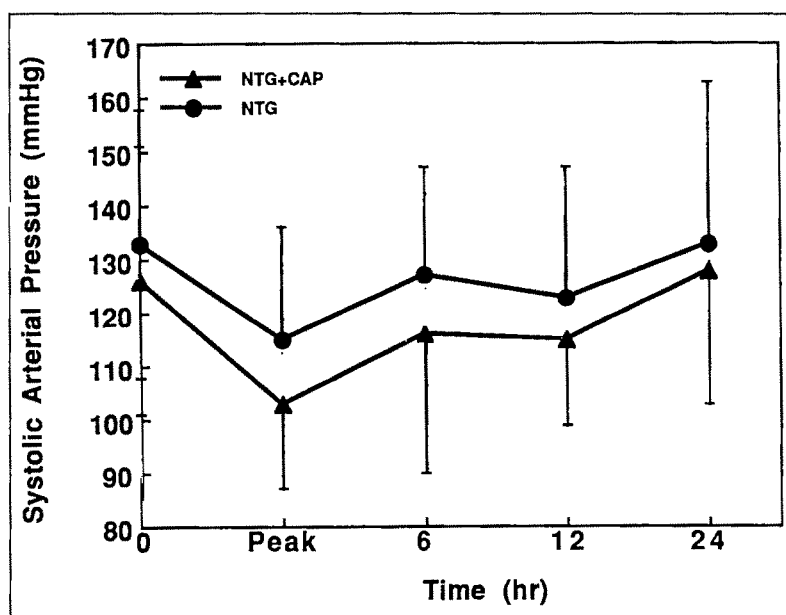


TABLE II Neurohumoral Measurements

	Group 1			Group 2		
	Control	24 Hours	p Value	Control	24 Hours	p Value
Plasma renin activity (ngAngI/ml/hr)	8 ± 11	8 ± 8	NS	18 ± 31	19 ± 20	NS
Aldosterone (ng/dl)	27 ± 32	34 ± 37	NS	24 ± 18	11 ± 10	NS
Body weight (kg)	62 ± 11	62 ± 9	NS	75 ± 10	75 ± 9	NS

ngAngI = nanograms of angiotensin I; NS = not significant.

The response of the renin-angiotensin system to nitroglycerin may be complex. The sudden decrease in right- and left-sided cardiac filling pressures reduces atrial natriuretic peptide and favors an increase in plasma renin activity,^{6,21} while improvement in cardiac output and juxtaglomerular blood flow would produce the opposite effect. Since the major effect of nitrate therapy is to reduce atrial pressures, with a more variable effect on cardiac output,^{22,23} nitroglycerin usually increases plasma renin activity at 4 to 6²¹ and possibly at 24

hours.⁴ Hyperreninemia, associated with an increase in angiotensin and aldosterone, may produce sodium and water retention, and has been invoked as a possibly important mechanism in the development of nitrate tolerance.⁶ It is noteworthy, however, that there was no increase in the already high plasma renin activity and body weight at 24 hours in the present study.

Angiotensin inhibition and nitrate tolerance: The present study showed that administration of captopril, in a dose sufficient to increase plasma renin activity and

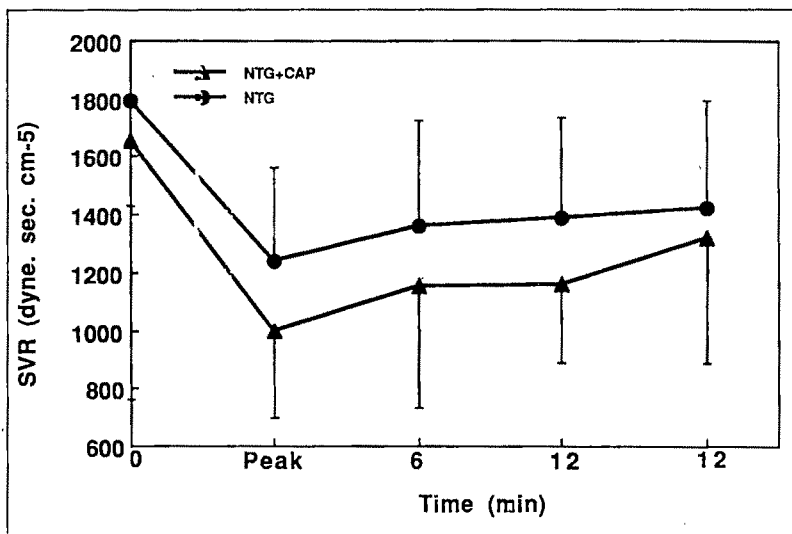


FIGURE 5. Systemic vascular resistance (SVR) during administration of nitroglycerin in patients receiving (NTG + CAP) and those not (NTG) receiving captopril. There was no difference between the 2 patient groups. SVR tended to be lower throughout in the captopril group.

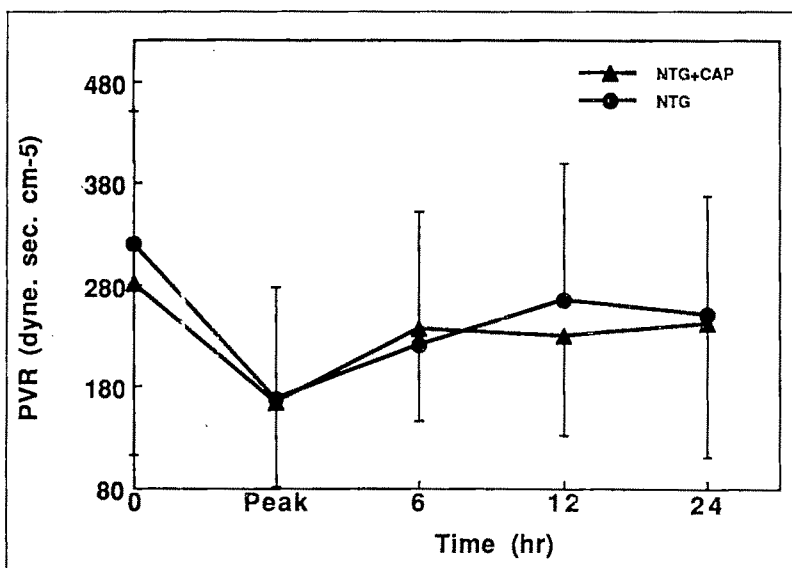


FIGURE 6. Pulmonary vascular resistance (PVR) during administration of nitroglycerin in patients receiving (NTG + CAP) and those not (NTG) receiving captopril. There was no difference between the 2 patient groups.

reduce plasma aldosterone, failed to alter the response of the patients to intravenous nitroglycerin and did not alter the incidence or extent of nitrate tolerance, neither with regard to right- or left-sided cardiac filling pressures nor with regard to systemic and pulmonary vascular resistance and cardiac output. Although the findings do not exclude counter-regulatory neurohumoral activation in the development of nitrate tolerance, the study implied that this mechanism was of little importance in the doses used in the clinical management of patients with severe CHF.

Since nitrate tolerance may be related to a biochemical mechanism in which depletion of sulfhydryl groups limits the production of S-nitrosothiols,⁵ it may be expected that captopril, a sulfur-containing compound, may alter the extent of tolerance at a cellular level. Nitrate tolerance can largely be reversed by the administration of large doses of the sulfhydryl donor N-acetylcysteine¹³ or methionine.²⁴ Measuring forearm blood flow, Levy et al²⁵ found that captopril diminished the tolerance to transdermal nitroglycerin patches. Their results may reflect the relatively small dose of nitrates in relation to a larger dose of angiotensin-converting enzyme inhibitor. Alternately, mechanisms in the peripheral venous bed may be different, particularly in patients with severe CHF.

Combined therapy with nitrates and captopril in the management of congestive heart failure: The addition of nitrates to the therapy of patients receiving captopril produced a significant decrease in left- and right-sided cardiac filling pressures, with an effect no less than that achieved in patients who were given nitrate therapy alone. Since pulmonary arterial wedge pressure was maintained above 10 mm Hg, cardiac index did not decrease during administration of nitroglycerin, even though nitroglycerin produced some withdrawal of the preload reserve mechanism.²⁶ Combined therapy with angiotensin-inhibiting drugs and nitrates is very useful in the management of patients with severe CHF.^{11,23} The study showed, however, that the mechanism of this salutary effect was not related to prevention of nitrate tolerance by the addition of captopril.

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Analysis of Different Methods of Assessing the Stenotic Mitral Valve Area with Emphasis on the Pressure Gradient Half-Time Concept

Bengt Wranne, MD, PhD, Per Ask, MSEE, PhD, and Dan Loyd, D Eng

There are 2 different theoretical models that analyze factors influencing the transmitral pressure gradient half-time ($T_{1/2}$), defined as the time needed for the pressure gradient to reach half its initial value. In this report the models and the assumptions inherent in them were summarized. One model includes left heart chamber compliance, the other does not. Although the models at a superficial glance seem to be contradictory, the conclusions drawn from them are similar: i.e., $T_{1/2}$ is influenced not only by valve area, but also by initial maximal pressure gradient and by flow. Different clinical situations in which the $T_{1/2}$ method for valve area estimation has been shown not to work are analyzed in the 2 models. It is concluded that these models have contributed to our understanding of the $T_{1/2}$ concept and when it should not be used. We also advocate use of the continuity equation in these situations, since no assumptions then need be made.

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The transvalvular pressure gradient across stenotic valves varies with blood flow. Therefore, when assessing the degree of stenosis, it is important to measure not only the gradient, but also the actual valve area. There are several ways of doing this, of which the continuity equation, relating the area to flow and flow velocity, and ultrasound 2-dimensional estimation of valve area, are the most straightforward. The Gorlin equation¹ is a special case of the continuity equation where flow velocity is replaced by pressure gradient according to the Bernoulli equation. Two-dimensional valve area estimation is beyond the scope of this study and will not be discussed further.

The pressure gradient half-time ($T_{1/2}$), defined as the time needed for the pressure gradient to reach half its initial value, was introduced for use during catheterization.^{2,3} It was adopted to Doppler ultrasound⁴ and, on empirical grounds, a simplified formula for assessing mitral valve area was suggested.⁵ Flow variations were not considered to influence the formula significantly at that time. The $T_{1/2}$ concept was later analyzed theoretically and experimentally by several investigators.⁶⁻¹¹ These reports agree that $T_{1/2}$ is influenced by initial pressure gradient as well as valve area. Some investigators⁷ claim that, in addition, transvalvular flow influences $T_{1/2}$, whereas others⁸⁻¹¹ claim that left atrial and ventricular compliances must be taken into consideration. This article analyzes different Doppler approaches to the estimation of stenotic mitral valve area, emphasizing the differences and similarities between these approaches (Figure 1).

DESCRIPTION OF THE VARIOUS APPROACHES

Analysis without inclusion of compliance: Flow through a stenotic valve is illustrated in Figure 2. The easiest and most obvious way to calculate mitral valve area is to apply the continuity equation to measured volume flow and flow velocity, or to noninvasively obtained stroke volume and Doppler velocity integral. We then obtain:

$$A_c = \frac{Q}{v} = \frac{SV}{DVI} \quad (1)$$

where Q is the volume flow, v the velocity, SV the stroke volume, and DVI the time integral of diastolic flow velocity through the valve. The area thus obtained is that of the vena contracta, A_c , where the fluid jet has minimal diameter, and which is normally located about half a diameter downstream from the anatomic orifice,

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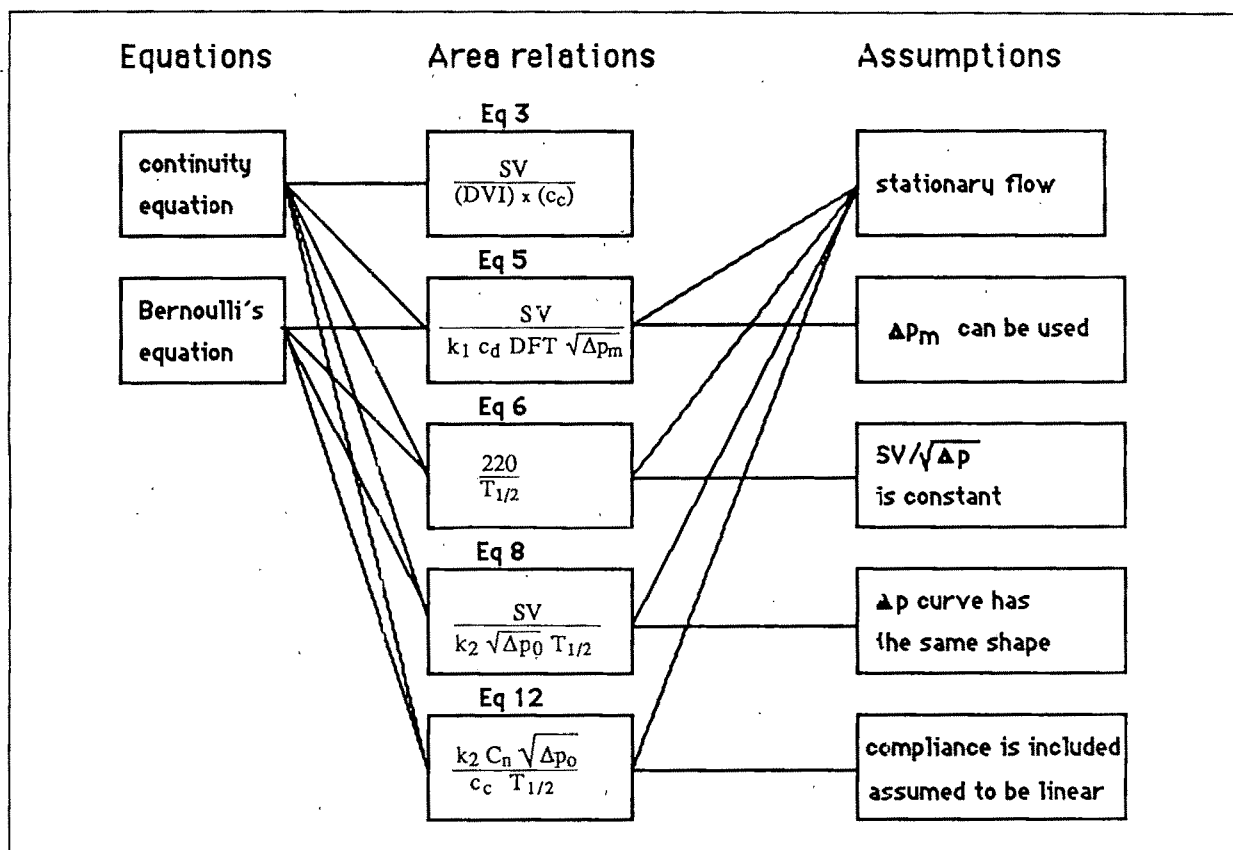


FIGURE 1. Different theoretical approaches to estimation of stenotic valve area, also illustrating the necessary assumptions made in each approach. Abbreviations are explained in the text in relation to the different equations.

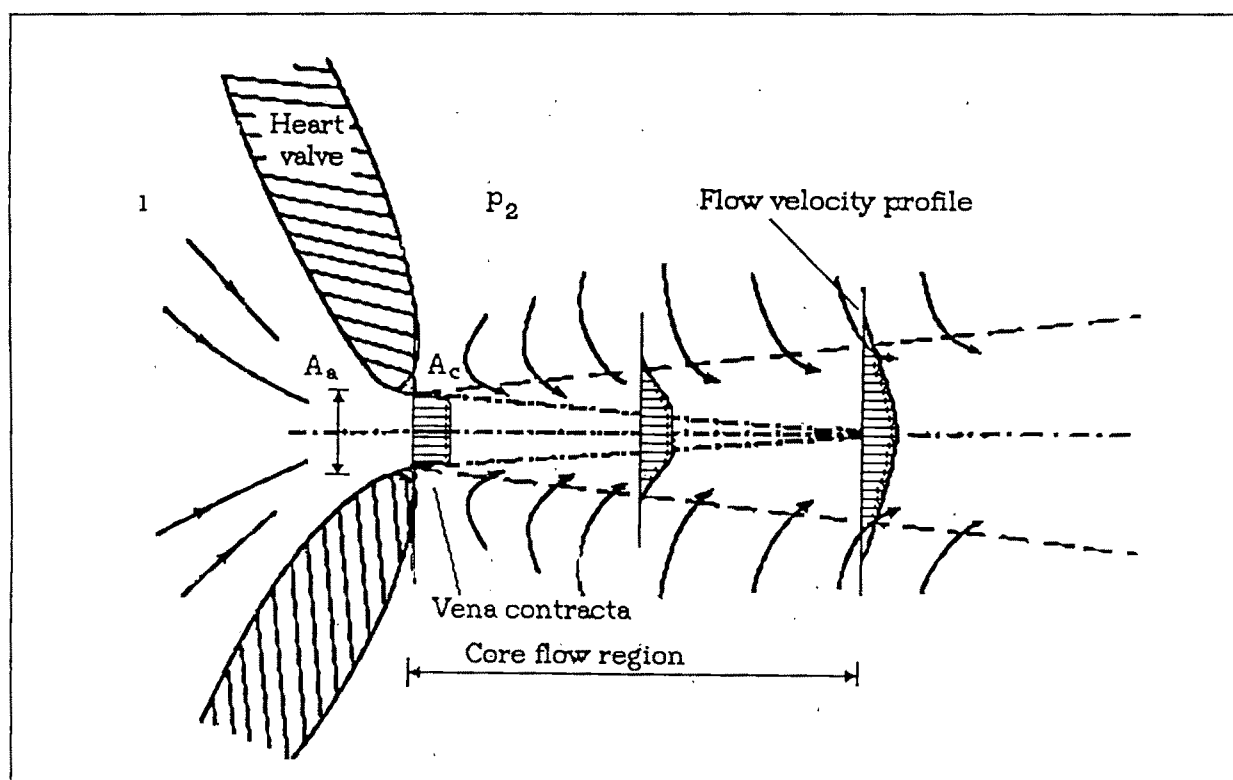


FIGURE 2. Flow pattern through a stenotic heart valve. A_a is the anatomic area of the valve and p_1 and p_2 are the pressures proximal and distal to the valve, respectively. At the entrance through the valve hole the flow contracts, and just distal to the hole, it reaches its minimal area, A_c , at the vena contracta. As indicated with the flow profiles, distal to the vena contracta is a core flow region with the same flow velocity as in the vena contracta.

A_a . The anatomic area can be obtained from the area at the vena contracta by division by the contraction coefficient, c_c .^{12,13}

$$A_a = \frac{A_c}{c_c} \quad (2)$$

Combining equations 1 and 2, one obtains:

$$A_a = \frac{Q}{(v) \times (c_c)} = \frac{SV}{(DVI) \times (c_c)} \quad (3)$$

This was realized by Gorlin and Gorlin¹ who, however, could not measure velocity. They therefore calculated velocity from the Bernoulli relationship and took friction into account via a velocity coefficient, c_v :

$$v = c_v \sqrt{\frac{2}{\rho} \Delta p} \quad (4)$$

where ρ is the density and Δp is the pressure gradient. Designating $\sqrt{2/\rho}$ with k_1 , setting $c_v \times c_c$ equal to the discharge coefficient, c_d ,^{12,13} replacing velocity with the square root of the mean pressure difference (subscript m), and combining equations 3 and 4, they got:

$$A_a = \frac{Q}{k_1 c_d \sqrt{\Delta p_m}} = \frac{SV}{k_1 c_d DFT \sqrt{\Delta p_m}} \quad (5)$$

which is the Gorlin equation. The Gorlin constant¹⁴ is therefore equal to $k_1 c_d$, the value of which depends on units used. DFT is the diastolic flow time, and $k_1 DFT \sqrt{\Delta p_m} \approx DVI$. A slight error is obtained in the Gorlin equation by estimating the velocity integral using $DFT \sqrt{\Delta p_m}$ instead of $\int \sqrt{\Delta p(t)} dt$. For severe stenosis this error is negligible, but for mild stenosis the area may be overestimated by up to 15%.

$T_{1/2}$, the time needed to reduce the transmitral pressure gradient to half its initial maximal value, was introduced for measuring the severity of mitral stenosis at catheterization^{2,3} and later adopted for Doppler ultrasound.⁴ On empirical grounds a simplified equation for the estimation of valve area in cm^2 was suggested⁵:

$$A_a = \frac{220}{T_{1/2}} \quad (6)$$

where $T_{1/2}$ is measured in ms. This equation does not include flow, and indeed it was initially thought that flow hardly influenced the area calculation.²⁻⁵

When analyzing the $T_{1/2}$ concept, Loyd et al⁷ predicted on theoretical and experimental grounds that, in addition to area, $T_{1/2}$ was influenced by transported volume and initial pressure gradient according to the following formula:

$$T_{1/2} = \frac{SV}{k_2 \sqrt{\Delta p_0} A_a} \quad (7)$$

which, solved for anatomic area, gives:

$$A_a = \frac{SV}{k_2 \sqrt{\Delta p_0} T_{1/2}} \quad (8)$$

where Δp_0 is the initial maximal pressure gradient and k_2 is a constant given by:

$$k_2 = \frac{c_d I_0}{a} \sqrt{\frac{2}{\rho}} \quad (9)$$

where I_0 and a are related to the shape of the pressure difference curve.⁷

Equations 5 (the Gorlin equation) and 8 can be compared with equation 3, which is based on the continuity equation. Because all these expressions have stroke volume in the numerator, the denominators of equations 5 and 8 are estimates of the diastolic time velocity integral.

Comparing the $T_{1/2}$ relation of equation 6 with equation 8, it is evident that equation 6 is a special case of equation 8 and applicable only when the relation $SV/(k_2 \sqrt{\Delta p_0})$ is constant. Both equations have the disadvantage that the calculations involve errors when the pressure gradient curve is truncated (as in short diastole).⁷

Analysis including compliance: In the analysis of mitral valve flow, Thomas et al⁸⁻¹⁰ used Newton's second law and the continuity and Bernoulli equations. The relations between volume and pressure in the atrium and ventricle were described by the atrial and ventricular compliances C_a and C_v , respectively. A schematic representation of the system is shown in Figure 3. In the derivation of $T_{1/2}$ it was shown that nonstationary and viscous terms could be ignored. They then arrived at a nonlinear differential equation. Assuming constant combined atrial and ventricular compliance, $C_n = C_a C_v / (C_a + C_v)$, the differential equation can be solved analytically, and the following expression for pressure difference is obtained:

$$\Delta p(t) = \left(\sqrt{\Delta p_0} - \frac{c_c A_a}{C_n \sqrt{2\rho}} t \right)^2 \quad (10)$$

For $\Delta p(t) = \Delta p_0/2$, t will be equal to $T_{1/2}$ and we obtain:

$$T_{1/2} = \frac{k_2 C_n \sqrt{\Delta p_0}}{c_c A_a} \quad (11)$$

and, if solving for the anatomic area,

$$A_a = \frac{k_2 C_n \sqrt{\Delta p_0}}{c_c T_{1/2}} \quad (12)$$

DISCUSSION

Is inclusion of compliance needed? In assessing $T_{1/2}$, the need to consider compliance has been suggested⁸⁻¹⁰ and refuted.⁷ At first glance these opinions, expressed in equations 7 and 11, seem to be contradictory. For example, the square root of the pressure difference appears in the numerator of equation 7 and the denominator of equation 11. However, in the simplified analysis used by Thomas et al,⁸⁻¹⁰ if compliance is treated as one total linear compliance, it can be estimated as $SV/\Delta p_0$. Replacing compliance (C_n) in equation 11 with this expression, $\sqrt{\Delta p_0}$ is transferred from the numerator to the denominator, which results in an expression essentially identical to equation 7. It can thus be

concluded that analyzing the $T_{1/2}$ concept both with and without inclusion of chamber compliance leads, with certain assumptions, to the same result. For a detailed description, see Appendix.

Characteristics of atrial and ventricular compliance:

The pulmonary circulatory system can be represented with hydraulic equivalents, the compliances of the pulmonary artery and vein and the flow resistance, mainly located in the capillaries.¹⁵⁻¹⁷ The venous compliance constitutes about 40% of the total, and the veins, from the hydraulic point of view, can be considered an integrated part of the left atrium.¹⁷ Because the time constant of the pulmonary vascular system, calculated from data by Shoukas,¹⁵ is approximately 1.9 second, and thus larger than typical values for $T_{1/2}$, pulmonary arterial compliance need not be included.

Ventricular diastolic characteristics are complex and include an early active relaxation and a late passive compliance phase.¹⁸ Combining the 2, ventricular compliance is generally considered to be nonlinear.¹⁹⁻²¹ The end-diastolic pressure/volume relation for the ventricle can be described by a function of the type $p = -a +$

$b e^c V$, where a , b and c are constants. It is apparent that compliance depends on ventricular filling (Figure 4).

Thomas et al⁸⁻¹⁰ serially combine atrial and ventricular compliances into 1 compliance. Strictly speaking, this can be done only if pressure/volume relation is linear and net compliance constant. Nevertheless, they end up with a resulting compliance that they consider constant. They explain this constancy by invoking an increase in atrial compliance and a decrease in ventricular compliance during left ventricular filling, resulting in an approximately constant compliance with transfer of blood from atrium to ventricle.

For constant compliance, equation 10 shows that there is a square relation between pressure difference and time. Since Bernoulli's equation relates pressure difference to flow velocity, this means that flow velocity decreases with the square root of pressure difference and thus linearly with time. If a linear decay in the mitral velocity curve is found, the total compliance can be treated as being approximately constant. This is true in most patients, showing that the assumption by Thomas et al⁸⁻¹⁰ is reasonable. In some patients, however, the velocity decay is nonlinear,²² suggesting that net compliance is not constant.

The case of constant compliance and linear flow velocity time decrease can be seen as a variant of the analysis presented by Loyd et al.⁷ As shown in the appendix, the 2 theoretical approaches for this case yield essentially the same expression for $T_{1/2}$. However, the theoretical analysis of Loyd et al.⁷ can also treat nonlinear pressure/volume relations (i.e., volume-dependent compliance) and, to some extent, include time-varying compliance. The limitation is that the pressure-difference curves must have the same shape for all cycles. If net compliance is constant these shapes are invariant, implying that this condition for the pressure curve shape also must be fulfilled for analysis in the way Thomas et al¹⁰ treat the problem.

Inflow to the pulmonary veins: Thomas,⁸⁻¹⁰ Karp,¹¹ and their co-workers treat the left atrium and pulmonary veins as a common chamber, but do not discuss the possible influence of inflow from the pulmonary veins. If inflow is substantial compared to outflow, atrial pressure changes cannot be calculated from compliance and outflow, which must be done for their analysis.

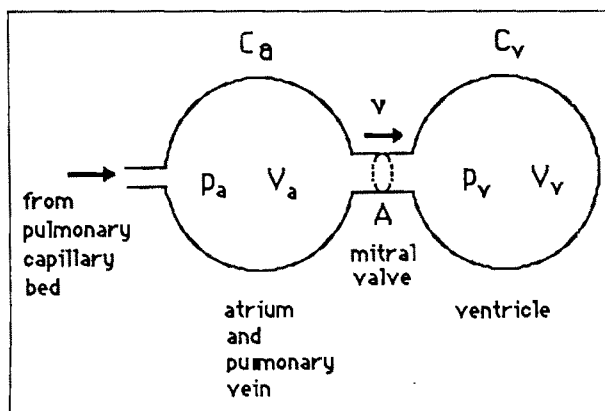


FIGURE 3. Representation of the mitral valve with the atrial-pulmonary system and ventricle; p_a and p_v are the pressures in the left atrium and ventricle, respectively; C_a = combined compliance of the left atrium and pulmonary venous system; C_v = ventricular compliance; V_a and V_v = corresponding volumes.

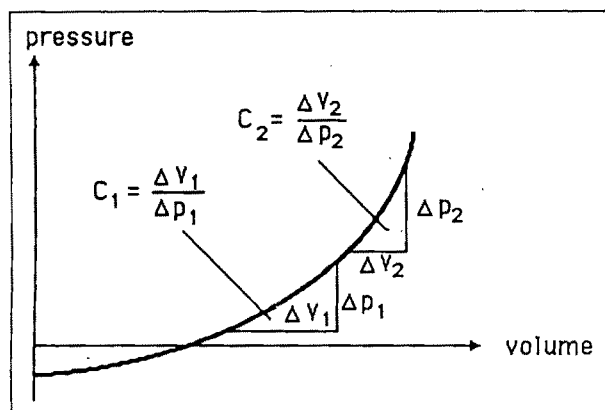


FIGURE 4. Principal shape of the nonlinear pressure-volume relation for the left ventricle during diastole. The figure illustrates dependence of compliance on the degree of ventricular filling. Compliance C_1 for a low diastolic volume is less than compliance C_2 for a higher volume.

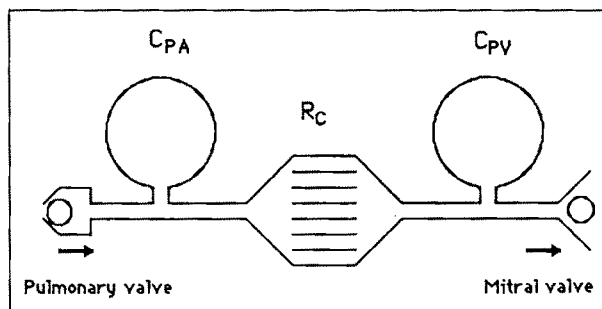


FIGURE 5. A hydraulic model of the pulmonary circulatory system. C_{PA} = compliance of the pulmonary artery; R_c = flow resistance of the pulmonary capillaries; $C_{PA} \times R_c$ = time constant of the system.

For a simplified analysis of pulmonary venous flow, we assume that inflow from the capillaries to the pulmonary veins is approximately constant throughout the cardiac cycle. Because of a high value for the time constant of pulmonary circulation (1.9 second, see before), fluctuations are damped out (Figure 5). The volume of blood transported from the capillaries to the pulmonary veins from onset of diastole until $T_{1/2}$ is reached equals $SV \times T_{1/2}/T$, where SV is stroke volume and T is length of the cardiac cycle. The relative error in estimation of volume in the ventricle will then be $T_{1/2}/T$. Thus, volume error for a normal $T_{1/2}$ of 60 ms at a cardiac cycle of 1,000 ms and stroke volume of 100 ml will be 6 ml; for a patient with prolonged $T_{1/2}$ of 200 ms, cardiac cycle length of 600 ms and stroke volume of 40 ml, it will be 13 ml. These values are negligible compared with a normal end-diastolic volume of 125 ml.

An advantage of the approach by Loyd et al,⁷ where the pressure-difference curve is assumed to have a certain shape, is the possibility of this curve including, to some extent, effects of pulmonary inflow to the system, because (in contrast to the model of Thomas et al⁸⁻¹⁰) flow is not estimated from initial pressure difference and compliance.

Effect of atrial contraction: None of the models expressly includes atrial contraction, although to some extent it can be incorporated into the model by Loyd et al⁷ as part of the assumed pressure-difference curve. For patients with severe or moderate stenosis this does not seem to be a major problem, since the relation between the expression $SV/(\sqrt{\Delta p_0} T_{1/2})$ (which multiplied by the constant k_2 gives an estimate of the valve area; compare equation 8) and the Gorlin-derived mitral valve area falls on approximately the same regression line irrespective of rhythm, implying a reasonably constant k_2 (Figure 6). This also implies that truncation of flow does not influence the relation to a major degree; if that had been true, a higher value of k_2 would have been expected. For sinus rhythm and mild stenosis, a dramatically different k_2 value seems to exist.

Use of steady flow equations: Loyd et al⁷ assume, on theoretical grounds, a stationary flow. Thomas et al^{8,10} started with a model including transient terms but showed that these terms could be excluded; in the final equations flow was treated as stationary.

Clinical situations where the pressure gradient half-time concept has been shown not to work: For certain groups of patients, the calculation of $T_{1/2}$ has errone-

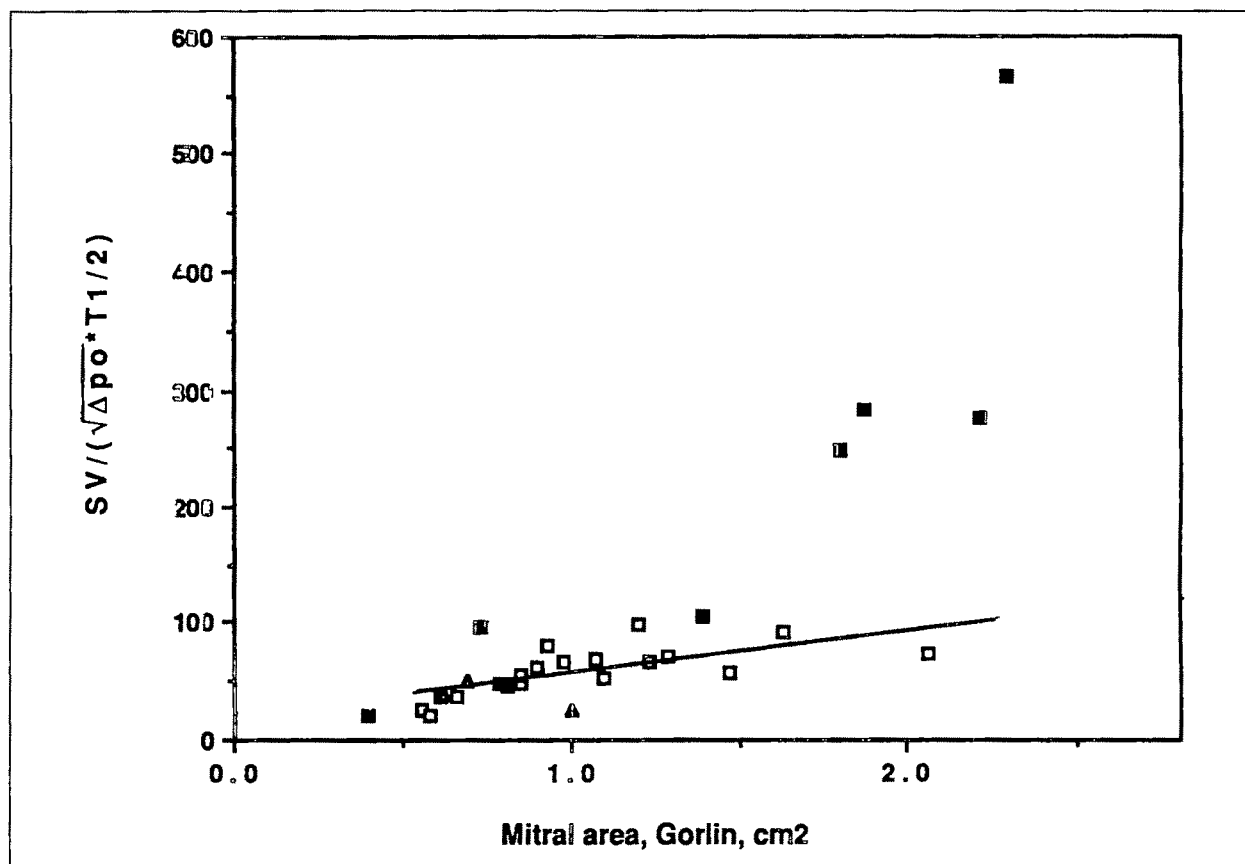


FIGURE 6. The relation between the expression $SV/(\sqrt{\Delta p_0} T_{1/2})$ (compare equation 8) and mitral valve area in 30 patients with mitral stenosis but without significant mitral regurgitation. All values were obtained during cardiac catheterization; $T_{1/2}$ and Δp_0 were measured from simultaneous pressure recordings from the left ventricle and the left atrium or the pulmonary wedge position. Stroke volume was obtained with the Fick principle. *Open squares*, patients with atrial fibrillation; *open triangles*, patients with nodal rhythm ($n = 1$) or electrical pacemaker ($n = 2$); *closed squares*, patients with sinus rhythm. The regression line shows the relation for patients with atrial fibrillation ($Y = 20.4 + 37.0 X$, $r = 0.68$). The slope of the regression line is the constant k_2 of equation 8, which is related to the shape of the pressure gradient decline curve. The relations for patients with mild stenosis and sinus rhythm are far off the regression line, indicating that k_2 may be different in these patients. Δp_0 = initial maximal pressure gradient; SV = stroke volume; $T_{1/2}$ = pressure gradient half-time.

ously indicated the degree of stenosis.^{7,9,11,23,24} The finding of a shorter than expected $T_{1/2}$ in patients with mitral stenosis and aortic regurgitation²³ may be explained by steep elevation of left ventricular diastolic pressure due to aortic inflow modulated by changed left ventricular compliance, mostly resulting in more rapid reduction in the transmitral gradient. Karp et al¹¹ explained a shorter than expected $T_{1/2}$ as being due to increased left ventricular stiffness (decreased compliance), which according to equation 11 lowers $T_{1/2}$. The finding of increased $T_{1/2}$ in a patient with mild mitral stenosis and ischemic heart disease⁷ seems to contradict this. However, the filling characteristics of the left ventricle are complex. The finding in this patient could hypothetically be explained by slow active relaxation in combination with fairly normal passive net compliance, while the shortened $T_{1/2}$ found by Karp et al¹¹ is due to a dominating change in net compliance. Similar changes in the diastolic filling pattern have recently been described in patients with cardiomyopathy, where shortened $T_{1/2}$ is seen with restrictive physiology and prolonged $T_{1/2}$ with impaired left ventricular relaxation.^{18,25} The contradictory findings^{7,11} thus express the complex situation that may exist with elevated transmitral driving pressure combined with compromised relaxation and compliance of the left ventricle with a pressure-volume relation that changes with preload. An immediate postvalvotomy $T_{1/2}$ higher than the expected⁹ may be explained by postvalvotomy increase in transported volume through the valve at a lower transvalvular gradient (equation 7), resulting in increased $T_{1/2}$ for a given area, or in terms of acutely altered net compliance (equation 11). Contradictory findings by Chen et al²⁴ show the complexity of the $T_{1/2}$ concept.

Practical implications: $T_{1/2}$ has one great advantage over other Doppler variables: it is independent of angle of incidence between blood flow and the Doppler beam. It clearly carries a relation to mitral valve area and should therefore be used as one of several criteria for assessment of mitral stenosis. Area calculation by the equation $220/T_{1/2}$ is, however, potentially dangerous because of its simplicity in combination with the magic impact a single number tends to have. One must always remember that $T_{1/2}$ also is influenced by stroke volume, initial pressure difference and compliance of the left heart chambers. $T_{1/2}$ should always be interpreted with this in mind; i.e., equation 8 should be conceptually considered. Special caution should be taken in patients who also have aortic regurgitation, impaired left ventricular function, or nonlinear transmitral velocity decay.

The denominator of equation 8, $k_2 \sqrt{\Delta p_0} T_{1/2}$, is an estimate of the diastolic time integral, and is also the denominator of the continuity equation (equation 5) and is easily measured from spectral Doppler recordings. By measuring stroke volume noninvasively,^{23,26,27} the continuity equation would seem advantageous to the $T_{1/2}$ approach, since the assumptions necessary for equations 8 and 12 are not needed. Analyses of flow conditions at the stenotic mitral valve with or without inclusion of compliance have given a theoretical base for understanding the limitations of the $T_{1/2}$ concept, but the presented equations (8 and 12) do not, for practical

purposes, have any advantages compared to the continuity equation.

Acknowledgment: We thank Inger Ekman and Joan W. Rosel for their help with manuscript preparation.

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APPENDIX

Consider the model of the atrium and ventricle in Figure 7. The atrium and ventricle are represented with open vessels of cross-sectional area A_1 and A_2 , respectively. A_0 is the area of the hole corresponding to the valve, and H the initial height difference between fluid levels. From the Bernoulli and continuity equations we can calculate $T_{1/2}$ as:

$$T_{1/2} = \frac{2 - \sqrt{2}}{\sqrt{2g}} \cdot \frac{A_1 A_2}{A_1 + A_2} \cdot \frac{1}{c_d A_0} \sqrt{H} \times \sqrt{1 + \left(\frac{c_d A_0}{A_1}\right)^2 - \left(\frac{c_d A_0}{A_2}\right)^2 + \left(\frac{c_c A_0}{A_1}\right)^2} \quad (A1)$$

where we can assume the value of the square root expression to be close to 1 if the relations between areas A_0 , A_1 and A_2 , respectively, are sufficiently small. This assumption will be made below.

The total volume transported by the initial height difference is:

$$V = \frac{A_1 A_2}{A_1 + A_2} H \quad (A2)$$

Including this expression in equation A1 and with the initial pressure difference equal to $\Delta p_0 = \rho g H$, we obtain:

$$T_{1/2} = (\sqrt{2} - 1) \sqrt{\rho} \frac{V}{\sqrt{\Delta p_0} c_d A_0} \quad (A3)$$

Solving for A_0 , we get:

$$A_0 = \text{constant} \frac{V}{\sqrt{\Delta p_0} T_{1/2}} \quad (A4)$$

which with $V = SV$ is essentially identical to equation 8.

From calculations of transported volumes we can obtain the combined compliance of the atrium and ventricle as

$$C_n = \frac{1}{\rho g} \frac{A_1 A_2}{A_1 + A_2} \quad (A5)$$

Inserting this expression in equation A1 and with the expression for Δp_0 , we get:

$$T_{1/2} = (\sqrt{2} - 1) \sqrt{\rho} C_n \sqrt{\Delta p_0} \frac{1}{c_d A_0} \quad (A6)$$

or, solving for A_0 , we get:

$$A_0 = \text{constant} \frac{C_n \sqrt{\Delta p_0}}{T_{1/2}} \quad (A7)$$

which is principally equal to equation 10.

This analysis shows that for the cardiac model described above, the valve area can be related to $T_{1/2}$ via expressions that either do or do not include compliance. It can be noted that the analysis by Loyd et al⁷ uses the discharge coefficient c_d , but that Thomas et al⁸⁻¹⁰ uses c_c . However, Thomas et al assumed the velocity coefficient to be equal to 1, and their c_c is therefore equal to c_d .

A detailed derivation of equation A1 can be obtained from: Loyd D, Ask P, Wranne B. Theoretical analysis of pressure half-time, Report LiTH-IKP-R588.

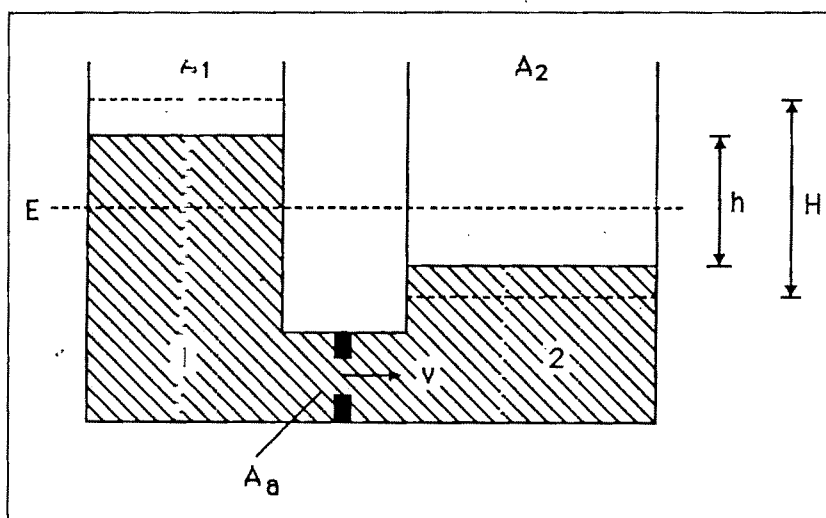


FIGURE 7. Flow through the mitral valve represented by flow between 2 fluid-filled containers. The atrial side is indicated by 1 and the ventricular side by 2. The cross-sectional areas of the containers are A_1 and A_2 , respectively. A_0 = area of the hole through which fluid flows with a flow velocity of v ; E = level of equilibrium; H = initial height difference of the fluid levels in the containers; h = the difference at a certain time.

Evaluation of Mitral Regurgitation by Cine Magnetic Resonance Imaging

Gerard Aurigemma, MD, Nathaniel Reichel, MD, Mark Schiebler, MD, and Leon Axel, PhD, MD, with the technical assistance of Christine Harris, RT, and Ali Muhammad

We used cine magnetic resonance imaging (MRI) to assess mitral regurgitation (MR) in 40 patients with coronary and/or valvular disease and 10 normal subjects and compared results to pulsed ($n = 30$) or color flow Doppler mapping ($n = 20$). Mitral regurgitation produced a dynamic signal void in the left atrium in systole in 15 of 16 patients with MR by pulsed Doppler and in an additional 15 of 16 patients whose MR was demonstrated by color flow Doppler. There were no false positives (sensitivity 94%, specificity 100% for both). The ratio of single-plane, maximal jet area to left atrial area was used to grade MR severity with mild defined as $<20\%$, moderate between 20 and 40% and severe $>40\%$. Cine MRI classification was identical to pulsed Doppler echocardiography in 26 of 30 patients and to color flow Doppler in 16 of 20 patients with no differences of >1 grade. Cine MRI consistently depicted smaller flow disturbances than pulsed Doppler (slope = 0.65) or color flow Doppler (slope = 0.60). Nonetheless, the cine MRI area ratio correlated well with pulsed Doppler ($r = 0.78$) and with color flow Doppler ($r = 0.74$). Thus, planar analysis of cine MRI in patients with MR of varying severity gave results that were similar to Doppler echocardiography. At present, for routine clinical assessment of MR, the benefits of cine MRI may be limited to patients in whom transthoracic Doppler echocardiography is not adequate.

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Cine magnetic resonance imaging (MRI) uses gradient refocused echoes to produce dynamic, high-resolution tomographic images of cardiac motion and blood flow without contrast administration.¹ The heart can be imaged at multiple levels simultaneously and the resulting images displayed in cine loop fashion. Moreover, turbulent flow associated with valvular regurgitation appears as a discrete signal void^{2,3} and is readily distinguishable from laminar flow. Pulsed and color flow Doppler echocardiography are used clinically for the evaluation of mitral regurgitation (MR), but can sample only selected planes through the heart.⁴ Because cine MRI can tomographically sample the entire cardiac volume and distinguish turbulent from laminar flow, it may be valuable to apply this technique to the study of MR. Our study assessed the ability of cine MRI to detect MR and to quantitate the size of the associated flow disturbance as compared to pulsed and color flow Doppler.

METHODS

Patients: Forty patients aged 25 to 88 years with a medical history of valvular or coronary artery disease and 10 volunteers aged 25 to 70 years without known heart disease made up the study group. Patients with known valvular heart disease were approached for participation in the study based on results of a recent Doppler echocardiographic examination or at the suggestion of their physician. In addition, patients with clinically normal valves who had a cine MRI examination for evaluation of coronary artery bypass graft patency⁵ were also included in the study group. All subjects were clinically stable, in regular sinus rhythm and gave informed consent. The study was approved by the institutional review board of the Hospital of the University of Pennsylvania.

Cine magnetic resonance imaging technique: MRI was performed in a 1.5 Tesla Signa (General Electric) MRI system. Each study began with electrocardiographically-gated multislice coronal spin echo images of the thorax for cardiac localization. The image matrix was 128×256 , interpolated to 256×256 for display and the field of view was 32 or 40 cm depending on patient size. The coronal series was used to define the extent of the left atrium. At least 2 cine MRI series of two to four 5 to 10 mm-thick axial slices through the left atrium and left ventricle with interslice distances of 5 mm to 2 cm were obtained in all subjects. Early in the series, however, we concluded that the optimal imaging approach consisted of interleaving 3 sets of three 10

mm-thick slices with an interslice distance of 20 mm per series; this approach was used routinely for the patients in the remainder of the series.

The cine MRI techniques used flip angles of 30° and gradient refocused echoes with an echo time of 12.5 ms and repetition time of 22 ms. The radio frequency pulse, readout gradient, phase-encoding gradient and slice-selective gradient occurred independently of the cardiac cycle every 22 ms. The R wave of each electrocardiographic cycle controlled advancement of the phase-encoding gradient to the next image line. In this study, frame rate was determined by dividing the RR interval by the repetition time and then by the number of slices desired in the cine loop. Thus, for an RR interval of 800 ms (heart rate 75 beats/min) 36 frames were available. If 3 slices were desired, each cine loop contained 12 frames per cardiac cycle. The number of frames per cardiac cycle for subjects in this series ranged from 5 to 26. It is also possible to obtain more frames by interpolation in the image reconstruction. Two to 4 signal averages per image series were obtained to optimize image quality. Each acquisition took 128 cardiac cycles, 1 for each Y line in the image. Time per acquisition at the time of this study included 2 to 3 minutes for prescan, 3 to 5 minutes for imaging and 5 to 10 minutes for imaging processing. Total time per study was approximately 50 minutes. Subsequent software improvements permit patient time in the system of roughly 35 minutes with image reconstruction time of 3 minutes per series.

		cMRI			
		0	Mild	Mod	Sev
PD	0	⋮⋮⋮			
	Mild	•	⋮⋮		
	Mod		••	⋮⋮	
	Sev			•	•

		cMRI			
		0	Mild	Mod	Sev
CFD	0	••••			
	Mild	•	⋮⋮		
	Mod		••	••••	
	Sev			•	•

FIGURE 1. Cine magnetic resonance imaging (cMRI) jet area/left atrium classification compared to pulsed Doppler (PD) and color flow Doppler (CFD). Mild was defined as an area ratio <20%, moderate as 20 to 40% and severe as >40%. Classification was identical in 42 of 50 cases overall with no differences of >1 grade.

Doppler techniques: Thirty subjects were evaluated using standard 2-dimensionally guided pulsed Doppler mapping of MR using commercially available systems. A 2.5 MHz Doppler flow probe was used to perform examinations from apical and parasternal windows. A point-by-point meticulous search for disturbed flow was conducted from apical 2- and 4-chamber and parasternal long-axis views in all patients. Twenty subjects were evaluated using color flow Doppler mapping with a Hewlett-Packard model 77020 system. A careful search was made in each view to record the maximum systolic left atrial area of disturbed flow.

Evaluation of results—cine magnetic resonance imaging: Qualitative recognition of MR by cine MRI was arrived at by consensus at a reading session attended by 2 cardiologists and 2 radiologists. Jets of MR were defined as dynamic zones of signal void in the left atrium in systole extending from the mitral valve plane. For each study, the cine MRI frame showing the maximal signal void associated with MR was selected. Quantitation was performed by digitizing the area of the signal void and the left atrial area from film hard copy using a microcomputer equipped with a backlit, transparent high-resolution digitizer (Hewlett-Packard 9825A). Because the imaging planes were different by cine MRI and Doppler echocardiography, the ratio of maximal jet area to left atrial area was used to normalize results. Severity was graded as follows: mild, jet area to left atrial area ratio <20%; moderate, jet area to left atrial area ratio between 20 and 40%; and severe, jet

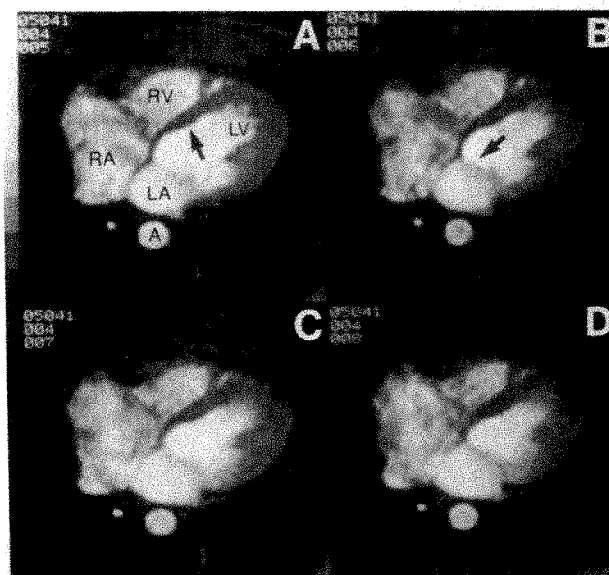


FIGURE 2. Four consecutive systolic axial magnetic resonance images taken from study of a normal volunteer at level of the mitral valve. **A**, arrow points to interventricular septum. There is uniform high signal throughout all 4 cardiac chambers and in the descending aorta. Myocardial structures have attenuated signal compared to blood pool. Moderator band is visualized in right ventricle. **B**, arrow points to closed mitral valve. **C** and **D**, in later systole, uniform high signal persists in left atrium and systolic septal thickening is also shown. A = descending aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

area to left atrial area greater than 40%, after the work of Helmcke et al.⁴

Doppler echocardiography: Qualitative recognition of MR by Doppler echocardiography was determined by 2 observers who were unaware of the cine MRI results. A single observer, blinded to the cine MRI results, assessed the severity of MR. Mitral regurgitation was defined as a broad high-velocity spectrum with aliasing detected in the left atrium and extending from the valve plane in systole for pulsed Doppler. Using color flow Doppler, MR was defined as a retrograde flow region with or without variance and aliasing extending from the mitral valve into the left atrium in systole and confirmed by pulsed Doppler. The area of the MR color flow disturbance was outlined on clear plastic film and digitized. In subjects who had pulsed mapping alone, a perimeter of the zone in the left atrium where turbulent flow was detected was made on a clear plastic overlay and digitized. The jet area to left atrial area was expressed as a ratio. The severity of MR was graded as mild if the ratio was <20%, as moderate if 20 to 40% and as severe if >40%.⁴

Statistical analysis: For the purposes of this study, Doppler echocardiography was taken as the reference standard. Sensitivity and specificity of cine MRI compared to color flow Doppler and pulsed Doppler were calculated. The classification of MR as absent, mild, moderate or severe by cine MRI and pulsed and color flow Doppler on single-plane maximum jet area left atrial area ratio was compared to define semiquantitative agreement. In addition, absolute jet area/left atrial correlations were compared by linear regression.

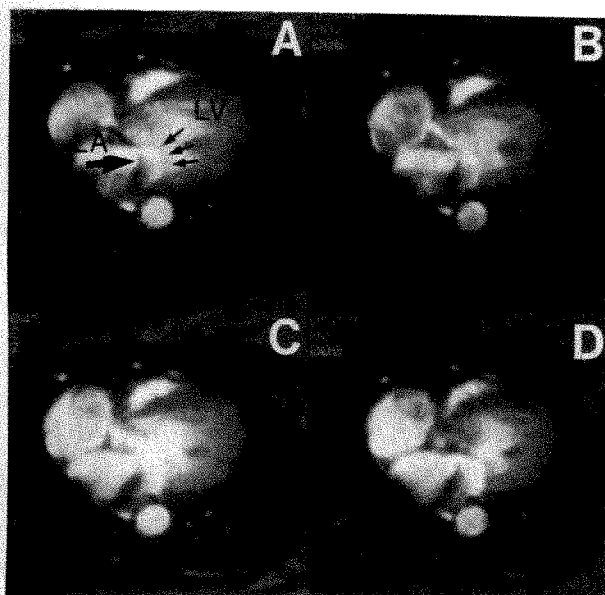


FIGURE 3. Axial cine magnetic resonance images taken from the study of a patient with moderate mitral regurgitation. Orientation is similar to Figure 2 for these systolic images. *A*, large arrow points to wedge-shaped signal void in left atrium directed posteriorly. Small arrows point to closed mitral valve leaflets. *B*, *C*, *D*, shape of signal void does not appear to change significantly in these systolic images.

RESULTS

Mitral regurgitation was detected by Doppler echocardiography in 32 of 50 subjects and by cine MRI in 30 of 50 subjects. Mitral regurgitation was found in 16 of the 20 subjects examined by color flow Doppler and 16 of 30 examined by pulsed Doppler (Figure 1). Cine MRI detected MR in 15 of 16 subjects with MR by pulsed Doppler and 15 of 16 with MR by color flow Doppler (Figure 1). There were no false positives. Overall sensitivity was 94% and specificity was 100% with Doppler flow mapping as a reference standard.

Using cine MRI, intracardiac laminar blood flow generates a higher signal than myocardial structures (Figure 2). A regurgitant jet of MR was visualized as a signal void in the left atrium in systole (Figure 3). The extent, shape and direction of the signal void varied from patient to patient. Also, there often was dynamic variation in the signal void size and shape in a single plane throughout systole (Figure 4).

Classification: Cine MRI classification was identical to pulsed Doppler in 26 of 30 (87%) with MR and identical to color flow Doppler in 16 of 20 (80%) subjects. There were no differences of >1 grade.

Jet area/left atrial area comparison: Figure 5 shows % left atrium occupied by the MR jet by color flow Doppler and cine MRI. The regression equation was cine MRI = $3.8 + 0.60$ color Doppler ($r = 0.74$). For pulsed Doppler, the relation was cine MRI = $4.6 + 0.65$ pulsed Doppler ($r = 0.78$) and is shown in Figure 6. Cine MRI, using the technique described, therefore consistently depicted a smaller relative area of flow dis-

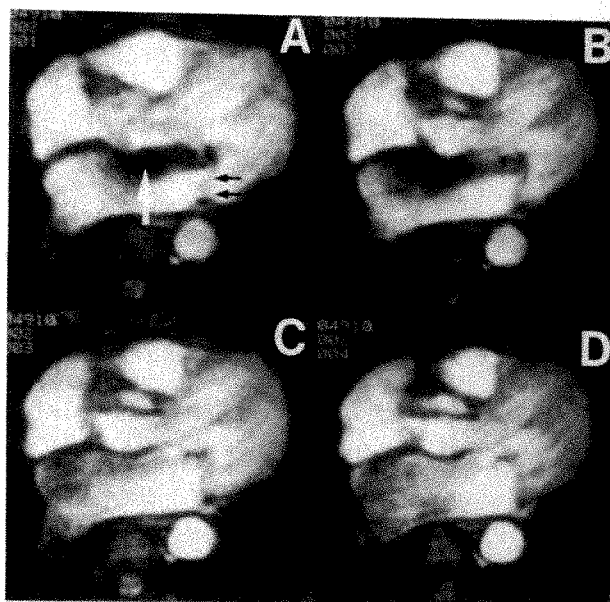


FIGURE 4. Axial systolic cine magnetic resonance images from study of a patient with severe mitral regurgitation. *A*, large white arrow points to signal void in left atrium emanating from region of closed mitral leaflets (small arrows). *B*, *C*, *D*, area of signal void enlarges and propagates medially and posteriorly throughout systole. In *C* and *D*, signal void has diminished in intensity but appears to occupy a larger percentage of the left atrial area, including pulmonary veins.

turbance when compared to pulsed or color flow Doppler mapping.

DISCUSSION

True volumetric estimation of the severity of valvular regurgitation can only be accomplished by comparing forward left ventricular stroke volume with total left ventricular stroke volume. Such estimates of regurgitant volume are only meaningful in patients with single-valve regurgitation. While the clinically accepted method for computing regurgitant volume subtracts Fick (or thermodilution) cardiac output from angiographic cardiac output,⁶ regurgitant volume has also been estimated noninvasively by radionuclide angiography⁷ and by cine computed tomography.⁸ In addition, 2-dimensional⁹ and Doppler echocardiography¹⁰ have been used to compare right and left ventricular stroke volumes and to estimate regurgitant fraction. However, for MR, clinicians commonly rely on semiquantitative assessment of the area of flow disturbance, such as is provided by Doppler echocardiography or by angiographic (1+, 2+) grading. In general, there is a good correlation between Doppler-derived regurgitant jet area and qualitative angiographic assessment of regurgitation.⁴ Because cine MRI, like color flow Doppler mapping, displays disturbed cardiac flow, it appears to be a suitable method for the semiquantitative grading of MR.

Cine magnetic resonance imaging signal properties: With gradient refocused imaging, myocardial structures

have attenuated signal relative to blood because their less mobile protons remain in the imaging plane and are continuously excited. The signal intensity of flowing blood depends, in part, on its velocity and on whether the flow is laminar or turbulent. In general, laminar flowing blood generates uniform, bright signal; this may be due to the continuous entry into the imaging plane of fresh blood whose spins are "unsaturated" and give maximal signal.^{1,11} Factors that may also contribute to the high signal are the high-proton density of blood² and the lack of phase cancellation induced signal loss and short echo times.

The regurgitant jet of MR was associated with loss of signal in a region of the left atrium in systole. Multiple mechanisms of signal reduction may exist. Dephasing of spins caused by shear between flow layers moving at different velocities adjacent to heart or blood vessel wall can produce a signal void. Time of flight effects are thought to be minimal for cine MRI. Fram et al¹² have shown the velocity dependence of signal amplitude at short repetition times in an in vitro model with evidence of a decrease in signal at higher velocities. For regurgitant jets, signal voids are presumably due to turbulence¹³; phase cancellation of signal may occur among protons moving at different velocities.²

Cine magnetic resonance imaging/Doppler comparisons: Overall qualitative correlation between cine MRI and Doppler echocardiography was good with no differences of >1 grade. The quantitative correlation was also good, though cine MRI appeared to show smaller flow disturbances that pulsed Doppler (slope = 0.65) or color flow mapping (slope = 0.60). This discrepancy may be due to multiple factors. First, temporal resolution of

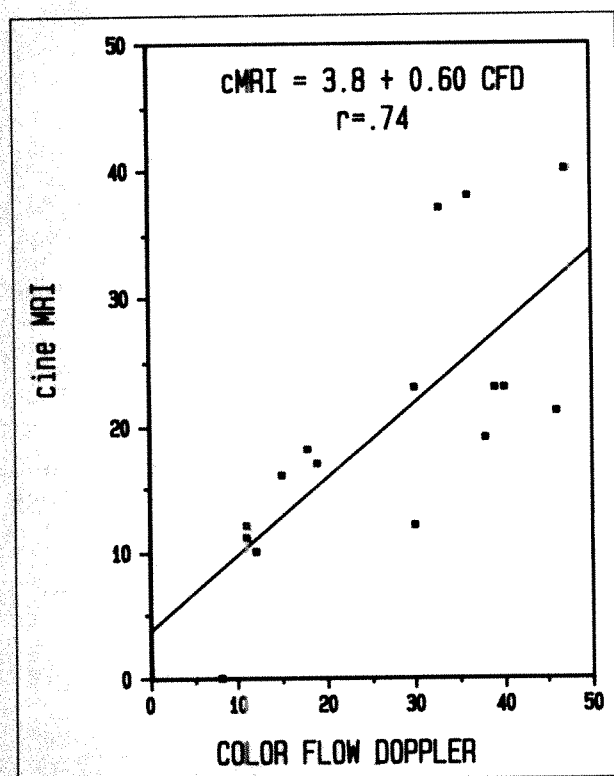


FIGURE 5. Comparison between jet area/left atrial area ratio (%LA) derived from color flow Doppler (CFD, x-axis) and from cine magnetic resonance imaging (cMRI, y-axis). cMRI = cine magnetic resonance imaging.

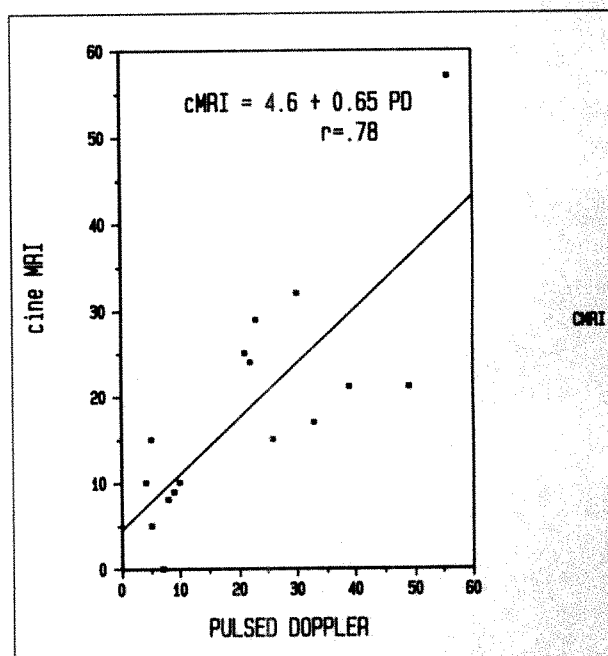


FIGURE 6. Comparison between jet area/left atrial area ratio derived from pulsed Doppler (x-axis) and from cine magnetic resonance imaging (cMRI, y-axis). cMRI = cine magnetic resonance imaging.

mapping was different for cine MRI than for pulsed Doppler. Thus, the maximal jet area defined for pulsed Doppler was mapped throughout systole and the composite of all points positive for MR were taken. Similarly, for color flow Doppler, the frame rates ranged from 15 to 30/second. In contrast, as noted before, cine MRI has an effective frame rate of only 12/cardiac cycle/slice in a 3-slice acquisition when the heart rate is 75 beats/min. Because MR flow varies over time, the differing temporal resolution of sampling by Doppler echocardiography could result in larger apparent jet area even if both Doppler echocardiography and cine MRI jets were actually identical. Secondly, differences in imaging planes used could affect the results, because axial cine MRI images lie closer to the short-axis plane of the MR jet, while the apical Doppler window lies closer to the jet's long-axis plane. Recent software enhancements permit oblique imaging with cine MRI and further studies should permit comparison of comparable image planes. Additionally, while Doppler and cine MRI both detect turbulent flow, they may in fact be measuring different physical phenomena. Finally, discrepancies between cine MRI and Doppler grading of MR may have been due to differences in loading conditions between the time of the 2 studies. Patients had their cine MRI and Doppler studies on the same day whenever possible. Nonetheless, because hemodynamic monitoring was not performed during MRI, hemodynamic changes, with attendant effects on regurgitant jet area, may have taken place.

Study limitations: There are a number of important limitations to this study. The size of the color flow Doppler jet of MR has been shown to vary depending on technical factors, including gain adjustment and filter settings.^{4,14} Technical factors also influence the size of the flow disturbance as depicted by cine MRI; the size of the signal void associated with valvular regurgitation appears to be dependent on echo time. In addition, as noted before, cine MRI frame rate is dependent on the patient's heart rate and number of slices per acquisition. Finally, window and threshold settings for the cine MRI display were set to provide maximum contrast for each image; no attempt was made to standardize these settings.

This study may also be criticized for the use of Doppler echocardiography as a reference standard. The limitations of Doppler semiquantitative grading have been well described.¹⁵ However, we chose to compare the results of cine MRI grading to Doppler echocardi-

ography because the latter remains the standard noninvasive method used to evaluate valvular regurgitation.

Acknowledgment: We wish to thank Kathleen Bogin, RN, and Margaret Dunlop, RN, for their patient recruitment and data management, Robert Morrow for his assistance in processing the Doppler data, the technical staff of the Devon Center for their assistance, and Janine Carter and Beverly Butler for their help in the preparation of the manuscript.

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Genetic Evidence of Dissociation (Generational Skips) of Electrical from Morphologic Forms of Hypertrophic Cardiomyopathy

Neal D. Epstein, MD, Henry J. Lin, MD, and Lameh Fananapazir, MD

The diagnosis of hypertrophic cardiomyopathy (HC) is traditionally based on the demonstration by echocardiography of left ventricular hypertrophy in the absence of apparent cause. This study reports on 5 adults in 4 families who are obligate or highly probable carriers of the HC gene by virtue of their position in the pedigree, but who have normal echocardiographic findings. Four of these 5 patients had abnormal signal-averaged electrocardiograms, a finding suggesting the presence of electrical disease despite the absence of left ventricular hypertrophy. The fifth patient, an identical twin of a patient with familial HC, had neither left ventricular hypertrophy nor a myocardial electrical abnormality. These data indicate that the spectrum of HC includes patients who have a potentially arrhythmogenic left ventricular substrate but who have no evidence of left ventricular hypertrophy. Our data demonstrating generational skips also imply that some instances of HC previously judged to be sporadic may indeed be familial.

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Hypertrophic cardiomyopathy (HC) is characterized by the demonstration of a hypertrophied nondilated left ventricle in the absence of other diseases that may cause an increase in left ventricular wall thickness.¹ Based on this definition, family studies have indicated a pattern of inheritance that is consistent with autosomal dominant transmission with variable penetrance and expressivity. Only 20 to 25% of first-degree relatives of patients with HC have echocardiographically demonstrable left ventricular hypertrophy, and nearly half the cases of HC appear to be "sporadic."²⁻⁹

Signal-averaged electrocardiographic detection of late potentials is strong evidence for the existence of a left ventricular substrate that can potentially sustain a reentrant ventricular arrhythmia.¹⁰ Because patients with HC are prone to ventricular arrhythmias and sudden death,^{11,12} it is significant that many of these patients have been shown to have late potentials.^{13,14} The first-degree relatives with normal echocardiograms of patients with HC also have a higher than expected prevalence of late potentials.¹⁵ This further supports the existence of an electrical form of HC in which left ventricular hypertrophy is absent. Consistent with this is the fact that occasionally children in affected families have an abnormal electrocardiogram with no evidence of left ventricular hypertrophy, and only later develop left ventricular hypertrophy in childhood or after adolescence.¹⁶ Therefore, many patients presumed to have the sporadic form of HC, may in fact be offspring of persons who have the gene for HC but who have no echocardiographic abnormality. The present study identifies 5 persons in 4 families who demonstrate these conclusions.

METHODS

Patients: Eighty patients with HC were queried for family histories that suggested the occurrence of generational "skips" in HC, i.e., incomplete penetrance or variable expressivity. Members of these selected families were then evaluated by 12-lead electrocardiography, echocardiography and signal-averaged electrocardiography.

Echocardiography: A Hewlett-Packard (Sonos 500 or Sonos 1000) real time, pulsed array, 90° ultrasonic scanner with a 2.5-MHz transducer was used to perform the echocardiographic studies. Real time studies were recorded at 60 frames/s. Two-dimensional echocardiographic images were obtained in a number of cross-sectional planes by using standard transducer positions. Using methods described previously,^{1,7,16} the distribu-

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tion of left ventricular hypertrophy was assessed primarily in the parasternal short-axis planes, although parasternal long-axis, apical 2- and 4-chamber views were also used to integrate the information obtained from the short-axis images.

In the short-axis plane, the left ventricle was divided into 4 regions that comprised the anterior and posterior ventricular septum and the anterolateral and posterior left ventricular free walls. Presence and extent of left ventricular hypertrophy in these 4 regions were evaluated in diastole at the level of the mitral valve and papillary muscle directly from the television monitor and with the aid of calipers. Thicknesses of the ventricular septum anteriorly and posterior left ventricular free wall also were assessed quantitatively from the M-mode echocardiogram.

A wall thickness index was used to assess the magnitude of left ventricular hypertrophy. This index was calculated by adding measurements of maximal wall thickness obtained in each of the 4 left ventricular segments.¹⁶ This calculated score has been used as a quantitative expression of the overall magnitude of left ventricular hypertrophy in patients with HC.¹⁶

Signal-averaged electrocardiography: Signal-averaged electrocardiography was performed using a high-resolution electrocardiogram (Predictor, Corazonix

Corporation). Signals were amplified, digitized and averaged to a noise level of $<0.4 \mu\text{V}$, using a selectable template for QRS detection and alignment, a bidirectional filter and high-pass corner frequencies of 25 and <0 Hz. A vector magnitude was plotted combining the filtered outputs of each lead. Late potentials were considered to be present when (1) the duration of the total filtered QRS complex was >110 ms, (2) root-mean-square voltage of the terminal 40 ms of the QRS complex (RMS) was $<30 \mu\text{V}$, and/or (3) duration of the low-amplitude ($<40 \mu\text{V}$) signals (LAS) was ≥ 35 ms.^{14,15}

RESULTS

Three pedigrees (families 2006, 2124 and 2817) were identified in which incomplete penetrance was evident on the basis of echocardiographic criteria. A fourth pedigree (family 2129) was identified in which incomplete penetrance was highly probable.

Family 2006 (Figure 1): The proband (no. 7) in this family underwent left ventricular myotomy and myomectomy at age 12 years. Her 15-year-old brother (no. 8) had echocardiographic evidence of HC. The proband's maternal great grandfather (no. 1) died before the first description of HC of a ruptured abdominal aortic aneurysm. He had always been normotensive as

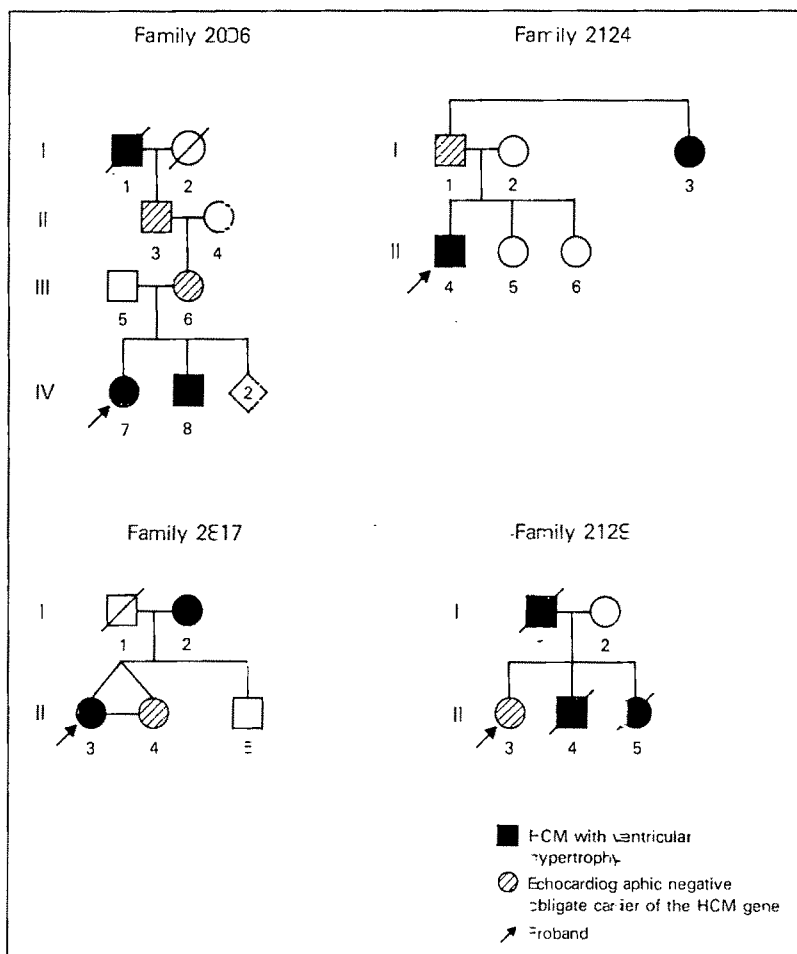


FIGURE 1. Inheritance of hypertrophic cardiomyopathy (HCM) in families 2006, 2124, 2817 and 2129. (Nonessential changes have been made to preserve family anonymity).

clearly documented by a physician involved in his long-term care. At autopsy, the heart weighed 570 g. The coronary arteries and valves were normal. The left ventricular wall measured 20 mm in thickness. Microscopic examination disclosed patchy areas of mild myocardial fibrosis and hypertrophy consistent with HC. All branches of the coronary arteries that were visualized were normal. Hemosiderin-laden macrophages in the lung indicated chronic cardiac disease. Both the grandfather (no. 3) and mother (no. 6) had normal echocardiograms and 12-lead electrocardiograms (Figure 2); however, both had abnormal signal-averaged electrocardiograms (Figure 3). There was no indication of HC in the spouses on echocardiography or by family history (nos. 4 and 5). These findings, and the presence of 2 affected siblings in the fourth generation and the affected great grandfather in the first generation, provide strong evidence for a genetic disease. Therefore, both the proband's grandfather (no. 3) and mother (no. 6), being positioned between 2 cases of HC in the first and fourth generations, can be considered obligatory carriers of the gene for HC despite their normal echocardiograms and electrocardiograms.

Family 2124 (Figure 1): In this family the proband (no. 4) had HC by echocardiographic criteria. His aunt (no. 3) also had HC on echocardiography and required a permanent pacemaker because of associated heart block. Cardiac catheterization showed that the coronary arteries were normal. The proband's father (no. 1) had no evidence of HC on echocardiography and had a normal electrocardiogram. His signal-averaged electrocardiogram was abnormal. There was no evidence of HC

in the proband's mother (no. 2) on echocardiography, 12-lead electrocardiography or family history. Thus, the proband's father (no. 1) is an obligate carrier for the HC gene and shows only an electrical abnormality detected by signal-averaged electrocardiography.

Family 2817 (Figure 1): The twins in this family (nos. 3 and 4) were judged to be identical at birth and were routinely mistaken for each other by teachers and acquaintances into their mid-twenties. We confirmed their monozygosity with a panel of 21 informative polymorphisms of serum proteins, red cell antigens and enzymes. These data, when used to calculate the probability that they are monozygous, give a result >99.99%.¹⁷ The proband (no. 3) in this family had significant left ventricular outflow tract obstruction and underwent left ventricular myotomy and myectomy for related symptoms resistant to medication. The proband's co-twin (no. 4) did not have HC by the echocardiogram, 12-lead electrocardiogram or signal-averaged electrocardiogram. The mother of the twins had HC as determined by an abnormal echocardiogram, 12-lead electrocardiogram and cardiac catheterization. The unaffected co-twin was therefore an obligate carrier of the HC gene.

Family 2129 (Figure 1): The proband's (no. 3) father (no. 1) died suddenly at age 35 with autopsy-proved HC. Two of his children (nos. 4 and 5) had echocardiographic findings of HC and died suddenly at age 16 and 22 years, respectively. The proband had a normal echocardiogram and 12-lead electrocardiogram. Several episodes of nonsustained monomorphic ventricular tachycardia (up to 15 beats, rate 160 beats/min)

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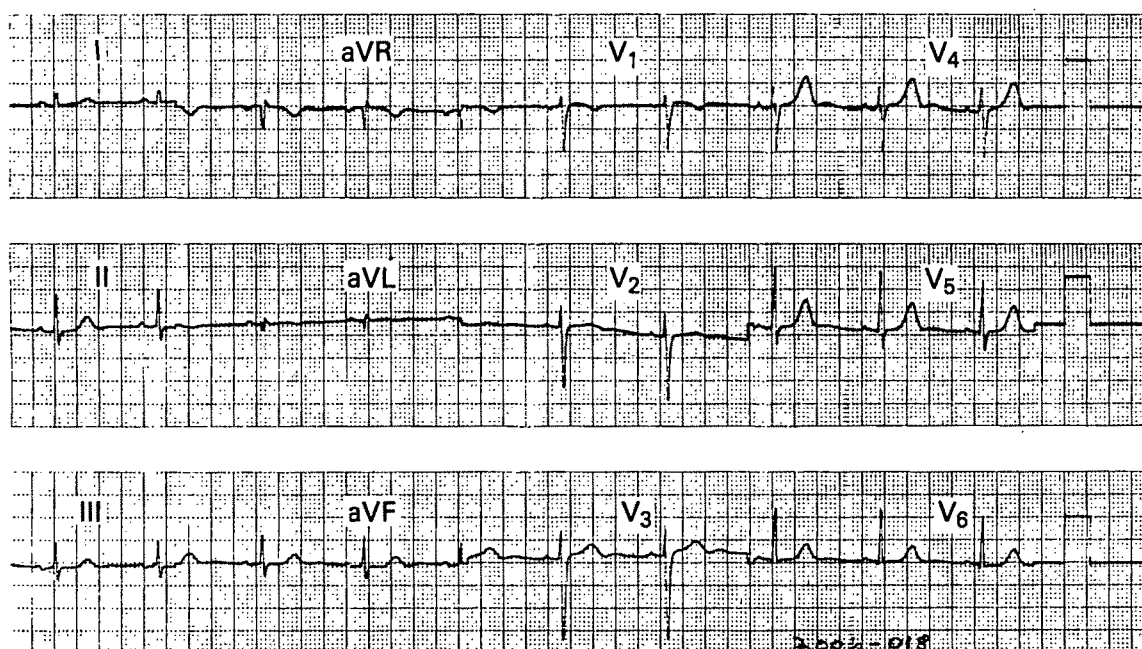


FIGURE 2. Normal 12-lead electrocardiogram in an obligate carrier of the hypertrophic cardiomyopathy gene (family 2006, no. 18). The patient had a normal echocardiogram but signal averaging showed presence of late potentials.

were documented by 48-hour Holter monitoring. Owing to several syncopal episodes, the proband underwent an electrophysiologic study; a sustained ventricular tachycardia was induced with 2 premature extrastimuli introduced at the right ventricular apical site following an 8-beat ventricular drive at a cycle length of 500 ms. This finding was regarded as abnormal. Although the proband is not strictly an obligate carrier of the HC gene (her young children have not been diagnosed with HC), it is highly likely that she carries the HC gene. Similar to the 3 patients mentioned, she demonstrated a dissociation of the morphologic abnormality from the electrical abnormality in familial HC.

DISCUSSION

The 4 pedigrees described demonstrate several points. The first 3 examples definitely identify obligate carriers of the HC gene who had no echocardiographic evidence of HC; the fourth pedigree is very likely another example, but the evidence cannot be considered definite. Thus, subjects may carry the gene but present no evidence of ventricular hypertrophy. Four subjects (in 3 families) who are obligate carriers of the gene and who have no echocardiographic evidence of left ventricular hypertrophy (family 2006, nos. 3 and 6; family 2124, no. 1; and family 2129, no. 3) have evidence of an elec-

trical abnormality of the myocardium. This was detected by signal-averaged electrocardiography in 3 of the 4 subjects. The fourth subject (no. 3 in family 2129) had ventricular tachycardia on Holter monitoring and inducible ventricular tachycardia at electrophysiologic study. Thus, the evidence is compelling that electrical abnormalities can be the sole clinical manifestation of HC; i.e., electrical abnormalities can be dissociated from the ventricular dysmorphology of HC as detected by M-mode and 2-dimensional echocardiography.

The dissociation of electrical abnormalities from what has become the prerequisite feature of the disease, namely, echocardiographically detected left ventricular hypertrophy, has implications for both the clinical spectrum and the genetic transmission of the disease. Whereas HC is characterized by left ventricular hypertrophy with or without electrical abnormality, our findings indicate that carriers of the HC gene fall into 1 of 4 categories. At the mildest extreme, the carrier may have no detectable echocardiographic or electrical abnormality. The unaffected identical twin in family 2817 is such an example. At the other extreme, patients may have both left ventricular hypertrophy and malignant ventricular arrhythmias. The other 2 categories would consist of patients who have either left ventricular hypertrophy or myocardial electrical abnormality. This

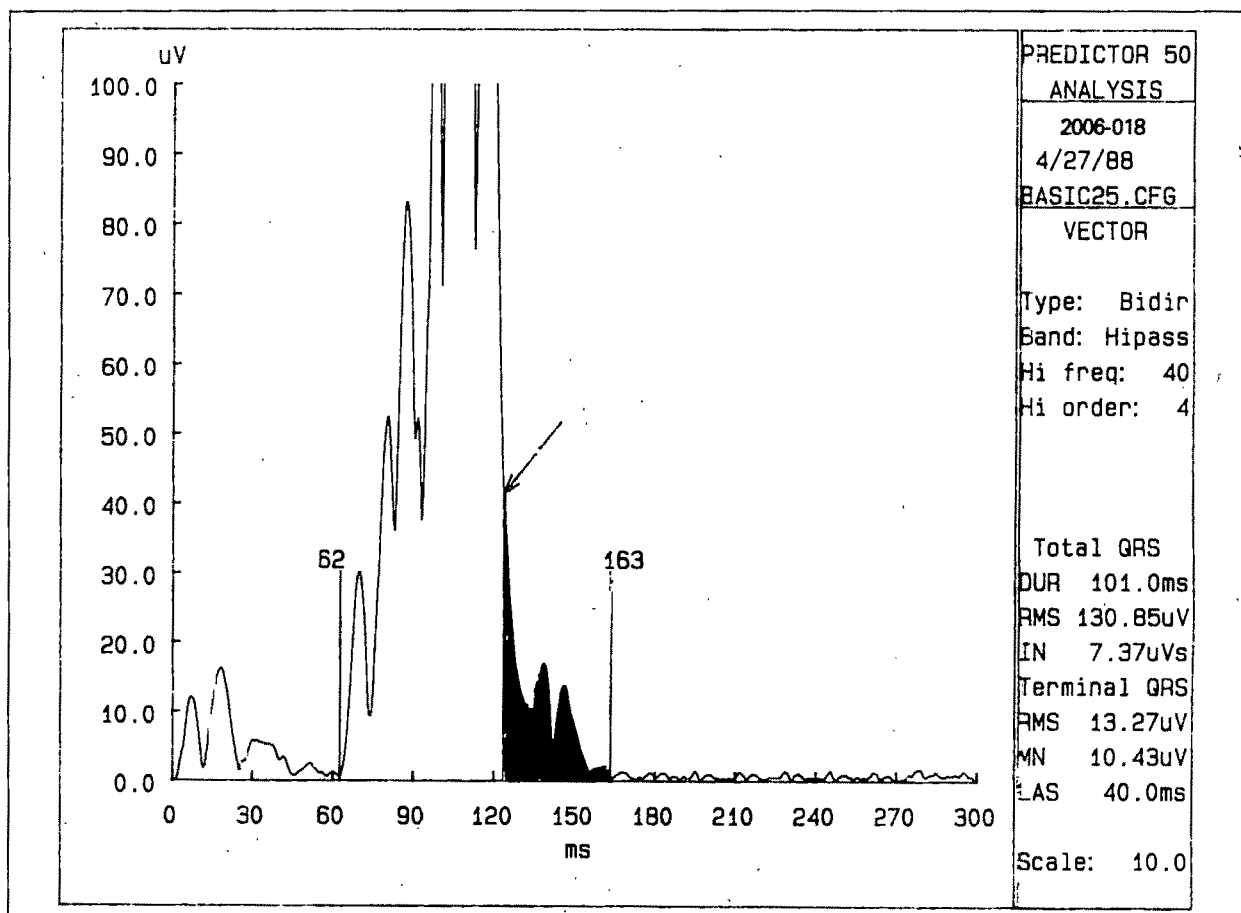


FIGURE 3. Abnormal signal-averaged electrocardiogram in an obligate carrier of the hypertrophic cardiomyopathy gene (family 2006, no. 18) who had no evidence of left ventricular hypertrophy by echocardiography. DUR = duration; IN = interval; LAS = low-amplitude signals; MN = mean; RMS = root mean square.

study identifies 4 persons in 3 families who have evidence only of myocardial electrical abnormality in the absence of ventricular hypertrophy. We believe that this may represent a form of HC with electrical dysfunction only. Definitive proof will require the use of molecular markers for HC. Such markers are currently being developed.¹⁸ Given the complexity of HC, it is clear why some instances of HC judged to be sporadic on the basis of unaffected parents may in fact be familial.

The diverse presentations of our patients demonstrate that the gene for HC is an example of a pleiotropic gene in that it has the ability to produce multiple phenotypic or clinical effects. Genetic disorders commonly demonstrate pleiotropy, and examples of such diseases affecting the cardiovascular system include the Marfan syndrome, Duchenne's muscular dystrophy and myotonic dystrophy.

The gene for HC also has autosomal dominant transmission with incomplete penetrance. Thus, there are obligate carriers of the gene who show no detectable features of HC. The unaffected twin is such an example. Although there is no good explanation for incomplete penetrance, there are other reports of discordance for a genetically determined trait in identical twins.¹⁹ Concepts such as germinal mosaicism,²⁰ a "two hit" process,²¹ or genetic imprinting²² have been offered as possible explanations in some instances.

Our findings have important implications for clinical management, genetic counseling and gene studies. We believe that subjects with a family history of HC should be screened for electrocardiographic abnormalities and arrhythmias as well as for left ventricular hypertrophy. Those showing electrical abnormalities without left ventricular hypertrophy may still carry the gene for HC. Members of families affected with HC who seek genetic counseling must be made aware that generational skips have been documented and that absence of left ventricular hypertrophy does not insure that the progeny will be unaffected. Finally, owing to the critical importance of disease assignment (phenotyping) in gene mapping, any prospective marker must be evaluated critically and corroborated in a number of families by several investigators in the field.

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One Heart, Two Bodies: Insight from the Transplanted Heart and Its New Electrocardiogram

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Cardiac transplantation provides a unique opportunity to record the electric field generated by a human heart in a new somatic environment. By examining pre- and posttransplantation electrocardiograms (ECGs), it is possible to address questions on the effect of rotation of the heart on its long axis on the surface ECG, the effect of thoracic anatomy on ECG voltage and predisposing factors for conduction defects observed after transplant surgery. To examine these questions, we reviewed a series of 35 matched donor and recipient ECGs. There were no differences in the mean height of the donors and recipients, but age, weight and body surface area were higher in the recipients ($p < 0.025$). We found no significant differences in the mean heart rate or precordial voltage but the PR and QT intervals were shorter ($p < 0.025$), and the precordial transitional zone was more to the left after transplantation ($p < 0.0005$). New evidence of right bundle branch delay was found in 11 recipients and this was not related to pretransplantation hemodynamic factors or the period of ischemic arrest. Thus, there is indeed an anatomic basis for the ECG determination of clockwise rotation of the heart when the precordial transition zone is to the left. Age and body habitus, per se, do not appear to affect precordial voltage and evidence of right bundle delay in the transplant recipient appears to be related to the altered position of the heart and not to injury or changes in right ventricular hemodynamics.

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With refinements in surgical techniques and better immunosuppression, successful transplantation of a human heart has become widely accepted and available.¹ The scalar 12-lead electrocardiogram (ECG) exhibits many changes after implantation of the new heart, most notably those related to electrical activity of the recipient atria, and has been used as a guide to the detection of graft rejection and silent myocardial infarction after transplantation.² While the electrophysiologic characteristics of the transplanted human heart have been well described, no systematic study of the change in the donor heart's ECG has been made after transplantation into the recipient.³ Cardiac transplantation provides a unique opportunity to record the electric field generated by a human heart in a new somatic environment. By observing pre- and posttransplantation ECGs, it is possible to address several questions of theoretical and practical significance, such as the following: the effect of rotation of the heart on its long axis on the surface ECG; the effect of thoracic anatomy on ECG voltage; and the possible predisposing factors for conduction defects commonly observed after transplant surgery. To examine these questions, we reviewed a series of matched donor and recipient ECGs, to evaluate a single human heart in 2 different living human hosts.

METHODS

We reviewed the files of 75 transplant recipients alive for ≥ 1 year for good quality donor and recipient 12-lead ECGs. Thirty-five donor ECGs, within 48 hours of donor heart harvesting, and 35 paired recipient ECGs, within 90 days (76 ± 20 days) of transplantation, were identified. Demographic data, as well as preoperative pulmonary pressures and pulmonary vascular resistance of the recipients, were also recorded.

Electrocardiographic analysis: The donor and recipient ECGs were read blinded to the age, sex and other clinical data.⁴ Conduction intervals were measured in the limb leads with similar leads used for both donor and paired recipients. The precordial transition zone was defined as the lead with the most equal deflections of R and S waves. Each of the 6 precordial leads was given a score of 10 and a position midway between the leads was scored as 5. Thus, a transition between V_2 and V_3 was scored as 25. Precordial voltage was measured by adding the deflection of the S wave in V_1 and the R wave in V_5 in millimeters. Right bundle branch block was defined as a QRS width of 120 ms or more, an RsR' complex in V_1 and a prominent S wave in V_6 .

TABLE I Demographic Data for Matched Donors and Recipients

	Donor	Recipient
	Mean (SD)	Mean (SD)
Sex (M/F)	25/10	32/3
Age (yrs)	22 (7)	46 (12)*
Height (cm)	171 (10)	174 (11)
Weight (kg)	65 (13)	71 (15) [†]
BSA (m ²)	1.74 (0.22)	1.84 (0.25) [‡]

* $p < 0.0005$; [†] $p < 0.005$; [‡] $p < 0.025$.

An incomplete right bundle branch block was defined as before with a QRS interval < 120 ms. Precordial voltage and transition zones were not calculated in the presence of right bundle branch delay. When serial donor ECGs were available, they were examined for reproducible precordial lead positioning and voltage and excluded if significant variability was evident. Posttransplant recipient ECGs were only used if there were no significant axis or voltage changes over a 6-month period of time.

Statistical analysis: The data are expressed as means with standard deviations. Groups were compared using a 3-tailed Student *t* test or chi-square analysis.

RESULTS

After screening the ECGs, 35 paired 12-lead scalar ECGs were available for analysis. The demographic data for recipient and donor hosts are listed in Table I. The mean standard electrocardiographic intervals for the donors and their matched recipients are listed in Table II. There was no significant difference in the mean heart rate or precordial voltage, but significant differences were found in the PR, QRS and QT intervals ($p < 0.05$). The precordial transition zone was more leftward (36 [9] vs 30 [9], $p < 0.0005$) compatible with clockwise rotation or a more posterior orientation of the transplanted heart.

There were 9 recipients with new incomplete right bundle branch block and 2 with complete right bundle branch block. The mean ischemic time, pulmonary arterial pressure and pulmonary vascular resistance were not significantly different in recipients with this conduction disturbance, when compared to those with a normal QRS (Table III).

DISCUSSION

The ECGs of 2 hearts in 1 chest as in heterotopic heart transplantation has been described.⁵ This is the first attempt to investigate some commonly used ECG

TABLE II Scalar Electrocardiographic Measurements in Donor and Recipient Hosts

	Donor	Recipient
	Mean (SD)	Mean (SD)
Heart rate (beats/min)	105 (24)	105 (17)
PR interval (ms)	147 (120)	138 (17)*
QRS interval (ms)	83 (11)	87 (12) [†]
QT interval (ms)	362 (49)	338 (32) [‡]
QRS axis (degrees)	63 (22)	51 (33) [‡]
Transition zone	30 (9)	36 (9) [§]
Voltage (SV ₁ + RV _{5,mm})	24 (9)	25 (10)

Calculation of the mean transition zone and precordial voltage is described in Methods section.

* $p < 0.025$; [†] $p < 0.05$; [‡] $p < 0.01$; [§] $p < 0.0005$.

anatomic criteria by analyzing ECG changes resulting after the transfer of a human heart to a second host.

Electrocardiographic criteria for clockwise rotation:

Wilson and Goldberger proposed that rotation of the heart on its long axis is the basis for certain ECG changes, principally movement of the "null point" on the precordial leads to the left or right.⁶ This concept was hotly disputed and to this day has remained moot.⁷ However, a transplanted heart is demonstrably rotated on its long axis after aortic and pulmonary anastomoses have been completed and this position is maintained because of the large mediastinal space that remains after the diseased heart has been excised. Chest radiography, as well as annual left ventriculography, also have confirmed this clockwise rotation.^{8,9} Rotation of the heart has been difficult to evaluate experimentally, although an elaborate model was reported using a perfused canine heart immersed in an electrolyte-filled human torso.¹⁰ Thus, in contrast to the contrived postmortem preparation of Grant⁷ and the aforementioned preparation, a true living human model of an incontrovertibly rotated heart is available. Over the normal heart, the R wave becomes taller and the S wave smaller as the electrode is moved from right to left across the chest. The transitional zone, the precordial area where the QRS is equiphasic, usually occurs at V₃, V₄ or in between. There was a highly significant leftward precordial shift in the transition zone in our transplant recipients (Figure 1), confirming that ECG criteria for clockwise rotation do have a true anatomic basis. Similarly, the frontal plane axis was significantly more horizontal, as expected from the position of the heart in its new host.

Voltage criteria for left ventricular hypertrophy in the young: Voltage remains the most important element in the diagnosis of left ventricular hypertrophy, but age

TABLE III New Right Bundle Branch Delay After Transplantation

	Bundle Branch Delay (n = 11)	No Bundle Branch Delay (n = 24)
	Mean (SD)	Mean (SD)
Ischemic time (min)	163 (38)	154 (58)
Mean recipient pulmonary pressure (mm Hg)	26 (13)	28 (8)
Mean recipient pulmonary arterial resistance (Wood units)	2.5 (1.2)	2.4 (1.5)

has been a substantial confounding factor.¹¹ Thus, normal limits for voltage diminish with age.^{11,12} No convincing explanation for this phenomenon has been forthcoming, but such variables as body size, thinner chest walls or other differences in habitus have been suggested to explain the increased voltages seen in younger subjects. The specificity of voltage criteria for left ventricular hypertrophy in adults is also affected by body habitus and complicating illnesses such as lung disease and pleural or pericardial effusions. We have found that when the hearts of younger patients are transplanted to older, larger recipients, the anticipated change in voltage is not seen. This would suggest that neither body size nor habitus and age, per se, are related to this ECG observation.

Right bundle branch delay after cardiac transplantation: Right bundle branch block, frequently incomplete, is not uncommon after successful cardiac transplantation (Figure 2). No adverse effects on survival or cardiac function have been reported. Possible explanations for this finding include an increased delay due to myocardial hypertrophy, right ventricular strain due to preexistent pulmonary hypertension in the recipient, or injury of the bundle during myocardial preservation and handling. Because the right bundle branch may more readily manifest relatively minor injury from ischemia, it is reasonable to suggest that right bundle branch block is a manifestation of the latter minor injury during harvesting of the donor heart. However, we did not find this to be so. Furthermore, there were no statisti-

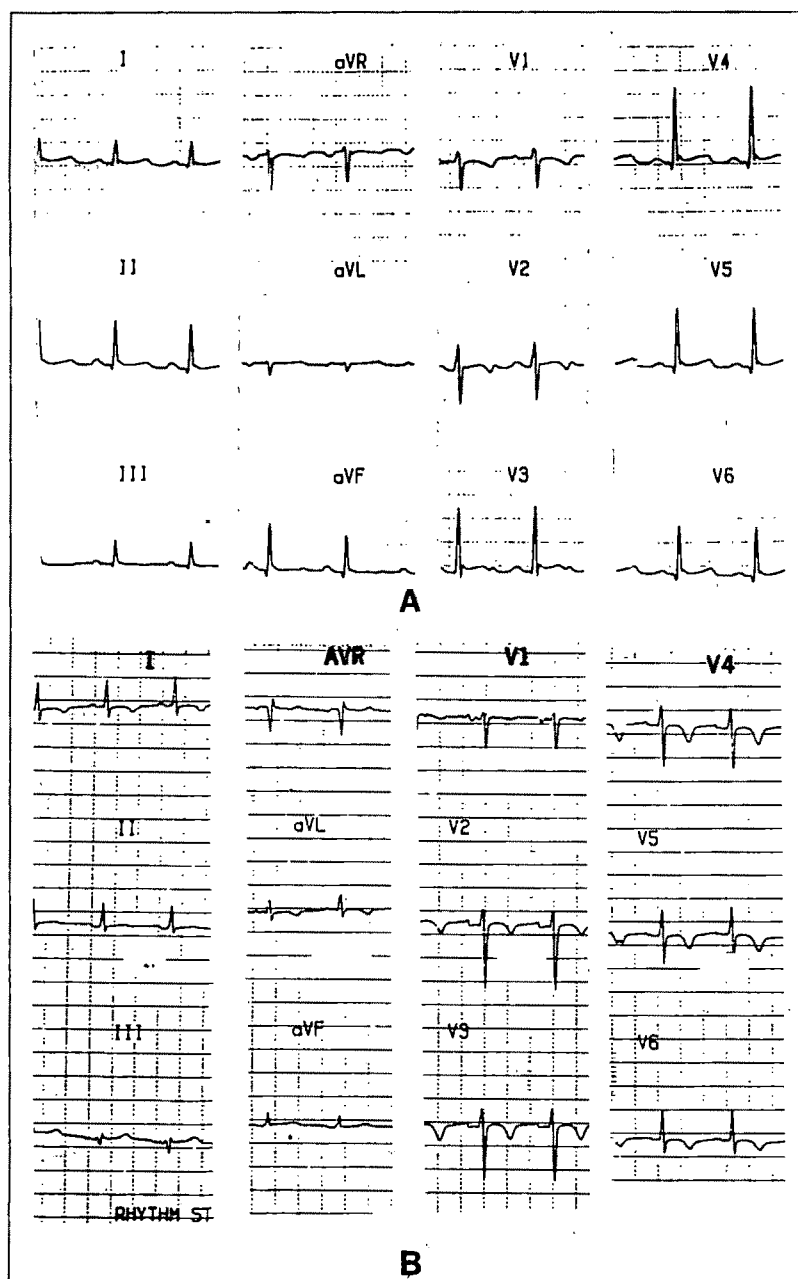


FIGURE 1. A, this 12-lead donor scalar electrocardiogram was obtained 24 hours before transplantation. B, the 12-lead electrocardiogram in the recipient 1 week after transplantation exhibits no significant change in precordial voltage, but a leftward shift in the transition zone and a more horizontal frontal plane axis is evident. Nonspecific T waves are also apparent.

cally significant differences in pulmonary vascular resistance between patients with and those without right bundle branch block, as previously reported.¹³ After cardiac surgery, right bundle branch delay is the most common conduction defect encountered, more common with valve than coronary bypass surgery, suggesting

that local injury is the mechanism involved.¹⁴ Transplant recipients have a more posteriorly or clockwise rotated heart than recipients without this finding and the presence of right bundle branch delay may actually reflect this abnormal cardiac position, as suggested by early experiments and recent studies.^{6,13}

Possible study limitations: While the same heart's ECG was recorded in 2 hosts and obvious changes including age, body size and sex have been tested, other differences between the hosts such as heightened autonomic tone and the effects of brain injury and death on the donor's heart and ECG, as well as denervation in the recipient, may also have affected various ECG intervals. Differences in cardiac volume affected by blood pressure and volume status have affected precordial voltage in various experimental studies, with precordial voltage and cardiac volume being inversely related; this may have had an influence on our findings.¹⁵ Immune activation in the recipient could result in changes in myocyte function and possibly ECG voltage as could significant pericardial effusions. We avoided ECGs during or soon after acute rejection episodes and it is unlikely that significant amounts of pericardial fluid were present in these stable patients >2 months postoperatively.

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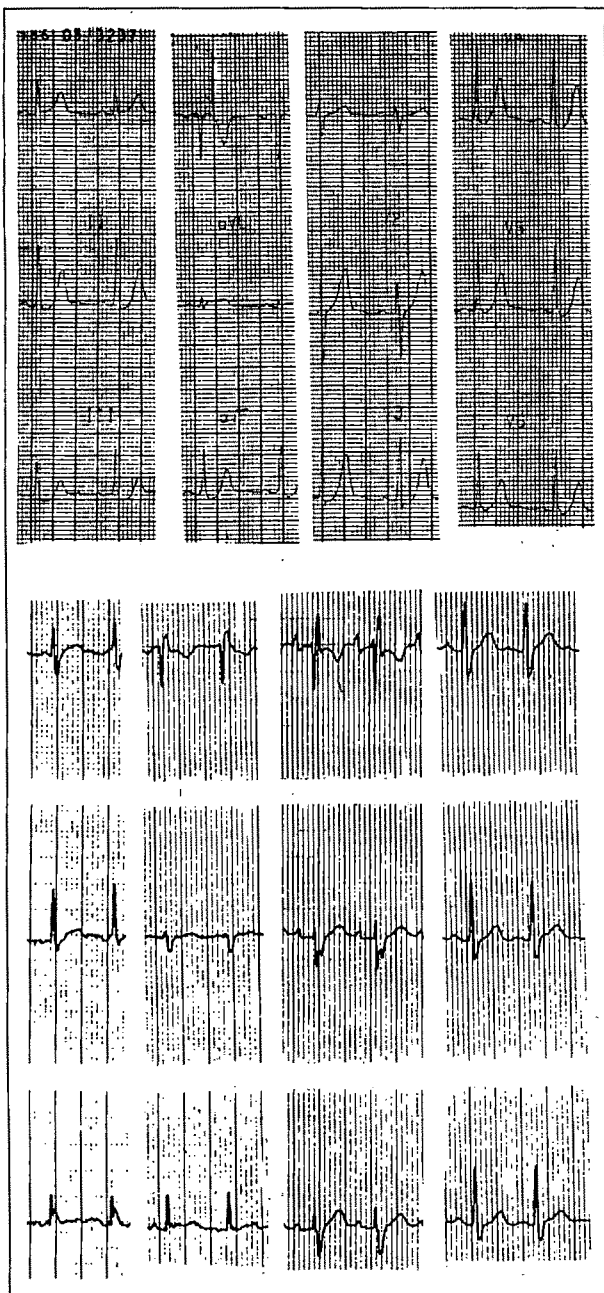


FIGURE 2. Top, this 12-lead scalar electrocardiogram was obtained 6 hours before transplantation. There is no evidence of intraventricular conduction delay. Bottom, the electrocardiogram in the transplant recipient now has evidence of new right bundle branch delay.

Effects of Bepridil and CERM 4205 (ORG 30701) on the Relation Between Cardiac Cycle Length and QT Duration in Healthy Volunteers

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Bepridil is a calcium antagonist that prolongs the duration of ventricular repolarization, whereas CERM 4205, another calcium antagonist, seems to be devoid of any effect on QT interval. The aim of this study was to compare the effects of bepridil and CERM 4205 on the QT-RR relation at different heart rates during rest and exercise and the results of pharmacologic tests designed to vary neurovegetative tone. Twelve healthy men (21 to 37 years) participated in a placebo-controlled, randomized, crossover, double-blind study and received either bepridil (200 mg/day twice daily) or CERM 4205 (200 mg/day twice daily), or matching placebo during three 14-day treatment periods at 2-week intervals. Bepridil but not CERM 4205, caused a significant prolongation of resting QT interval. The RR-QT relation was monoexponential for all subjects during resting and exercising physiologic conditions and remained unchanged after 14 days with placebo or CERM 4205. Bepridil significantly shifted the relation upward, resulting in a rate-dependent QT prolongation that predominated during bradycardia. After isoprenaline, QT no longer adapted to changes in heart rate, whereas atropine resulted in a rate-dependent shortening in QT. These results suggest that bepridil and CERM 4205 exert different effects on ventricular repolarization, since only bepridil significantly prolonged QT duration. Bepridil-induced prolongation of QT increased at slow heart rates, which could explain the greater incidence of torsades de pointes in bradycardia.

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Bepridil, (β -[(2-methylpropoxy) methyl] - N-phenyl - N-(phenylmethyl)-1-pyrrolidine-ethanamine monohydrochloride monohydrate), is a calcium entry blocker used as an antianginal agent.¹ Besides its vasodilating properties, bepridil has been demonstrated to be an effective antiarrhythmic agent.² By prolonging the duration of ventricular repolarization (QT interval on the surface electrocardiogram),²⁻⁵ bepridil poses the risk of torsades de pointes.⁶⁻⁷ CERM 4205* (1[(1-propenyl) cyclohexyloxy]-2-(1-pyrrolidinyl)-3[(2-methylpropoxy) propane hydrochloride) is another calcium antagonist that does not modify the duration of ventricular repolarization.⁸

The functional dependence of QT interval on the cardiac cycle length (RR interval) has recently been best described by an exponential formula, for a wide range of physiologic heart rates.⁹⁻¹¹ Furthermore, QT interval duration may also be altered by autonomic nervous system modifications; we previously showed that the physiologic adaptation of QT duration to cardiac cycle length was mainly under parasympathetic control.¹⁰ Therefore, it is of interest to study whether the lengthening in QT during bepridil or CERM 4205 therapy is influenced by heart rate. This study compares the effects of bepridil and CERM 4205 on the QT-RR relation at different heart rates during rest and exercise and the consequences of pharmacologic tests designed to vary neurovegetative tone in healthy volunteers.

METHODS

Patients: Twelve healthy male volunteers, mean age 27 years (range 21 to 37), participated in this study after screening by history, physical examination, 12-lead electrocardiogram, and routine laboratory tests of hematology and serum biochemistry to ensure good health. No subject had been taking any medication for 1 month before the study. This study was approved by the Ethical Review Committee of Saint-Antoine University Hospital and each subject gave informed written consent.

Study design: This study was a randomized, double-blind, 3-way crossover comparison involving three 14-day periods of treatment, each performed at least 2 weeks apart. Film-coated tablets of either CERM 4205 (200 mg/day twice daily), bepridil (200 mg/day twice

*CERM 4205 or ORG 30701.

daily) or matching placebo (twice daily) were orally administered from days 1 to 14 of each treatment period.

Heart rate, systolic and diastolic blood pressure and electrocardiographic intervals (PR, QRS and QT) were measured at rest, on day 0 (control period, before any drug administration), and on days 7, 14 and 15 (12 hours after the last drug administration) at minimum drug plasma concentration, just before the morning administration of the medication.

The QT-RR relations were studied on day 0 before the first dose and on the last day (day 15, 12 hours after the last dose) of each period. For these QT-RR relation studies, the subjects came to the Clinical Pharmacology Unit at Saint-Antoine hospital in the morning after having had breakfast with no tea or coffee and not having smoked for the last 12 hours. An indwelling catheter was inserted into an antecubital vein and normal saline solution was used to keep the catheter patent for 8 hours. Before the start of the study, a 12-lead electrocardiogram was recorded and blood pressure and heart rate were automatically measured (Dynamap, Riom Laboratories CERM, Saint-Denis, France). Then the QT-RR relation was studied during 2-hour supine rest, followed by a dynamic exercise test on a bicycle ergometer during which the work load was increased by 20 watts every minute until the subject reached the maximal theoretical heart rate for age. After 30 minutes rest postexercise, incremental intravenous bolus doses of isoproterenol (0.2 to 12.8 μg) were administered to each subject at ≥ 5 -minute intervals. This β -adrenergic stimulation was repeated 0.5 hour after an intravenous injection of atropine sulphate (0.04 mg/kg).

Drug plasma concentrations were measured on day 0 before any drug administration, and on days 7, 9, 11, 14 and 15 (12 hours after the last drug administration) before morning dosing in order to determine minimal plasma drug concentration.

To study the relation between changes in QT interval duration and plasma levels of drugs, resting electrocardiograms were recorded and plasma samples were simultaneously collected on day 14 at t_0 (before administration) and 0.25, 0.5, 1, 2, and 3 hours after dosing.

TABLE I Resting Cardiovascular Parameters on Days 0 and 15 of Each of the Three Treatment Periods

		Placebo	Bepridil	CERM 4205
Heart rate (beats/min)	D0	71 \pm 10	69 \pm 8	68 \pm 9
	D15	75 \pm 11	67 \pm 8	72 \pm 8
PR interval (ms)	D0	160 \pm 20	170 \pm 20	160 \pm 20
	D15	170 \pm 30	170 \pm 20	160 \pm 20
QRS interval (ms)	D0	100 \pm 10	100 \pm 10	100 \pm 10
	D15	100 \pm 10	100 \pm 20	100 \pm 10
QT interval (ms)	D0	390 \pm 20	400 \pm 30	390 \pm 20
	D15	390 \pm 30	450 \pm 30*	390 \pm 30
Systolic blood pressure (mm Hg)	D0	116 \pm 7	119 \pm 6	117 \pm 10
	D15	115 \pm 9	116 \pm 7	115 \pm 8
Diastolic blood pressure (mm Hg)	D0	67 \pm 9	66 \pm 8	67 \pm 8
	D15	67 \pm 8	65 \pm 8	65 \pm 11

* $p < 0.05$ compared with value during bepridil control period.
Values are expressed as mean \pm standard deviation ($n = 12$).
D = day.

Assay method: Bepridil and CERM 4205 were assayed in plasma by gas chromatography. The assay method for bepridil has previously been published.¹² For CERM 4205, the assay procedure included n-hexane extraction from plasma and gas chromatography with nitrogen selective detection. An analog of CERM 4205 was used as internal standard. The coefficient of variation of the assay was 10% at low concentrations (5 to 100 $\text{ng} \cdot \text{ml}^{-1}$) and equal to 3% at higher concentrations (500 to 1,000 $\text{ng} \cdot \text{ml}^{-1}$). The sensitivity of the method was 1 $\text{ng} \cdot \text{ml}^{-1}$ of plasma.

Electrocardiographic recordings: For the QT-RR relation studies, electrocardiograms were recorded at a paper speed of 50 mm/s (with a calibration of 20 mm/mV) over 5 consecutive beats at 15-minute intervals during 2 hours of rest (including forced inspiration and expiration, which were continuously recorded), and during the last 15 seconds of each exercise work load step. After pharmacologic interventions, electrocardiograms were recorded continuously from 15 to 60 seconds after each isoproterenol bolus intravenous injection, and over 5 consecutive beats at different times up to 30 minutes after the atropine injection. QT and preceding RR intervals were measured blindly in lead II by a single ob-

FIGURE 1. Changes in measured resting QT intervals over time during the 3 treatment periods ($n = 12$, mean \pm standard deviation). * $p < 0.05$ compared with values during bepridil control period.

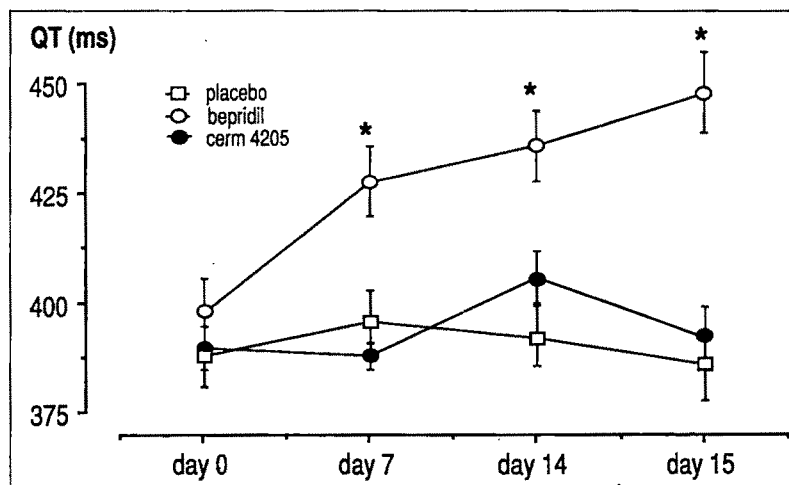


TABLE II Compare Mean Regression Parameters of Individual Exponential Equations $QT = A - B \cdot \text{Exp}(-k \cdot 10^{-3} \cdot RR)$ Between Days 0 and 15 During the Three Treatments

	Day 0			Day 15		
	A	B	k	A	B	k
Placebo	409 ± 24	900 ± 200	4.5 ± 1.1	421 ± 28	673 ± 169	3.7 ± 1.1
Bepridil	410 ± 22	795 ± 218	4.0 ± 0.9	478 ± 45*	798 ± 202	3.6 ± 1.7
CERM 4205	417 ± 15	697 ± 150	3.7 ± 0.7	423 ± 25	966 ± 610	4.1 ± 1.1

* $p < 0.05$ compared with values during bepridil control period.
Values are expressed as mean ± standard deviation ($n = 12$).

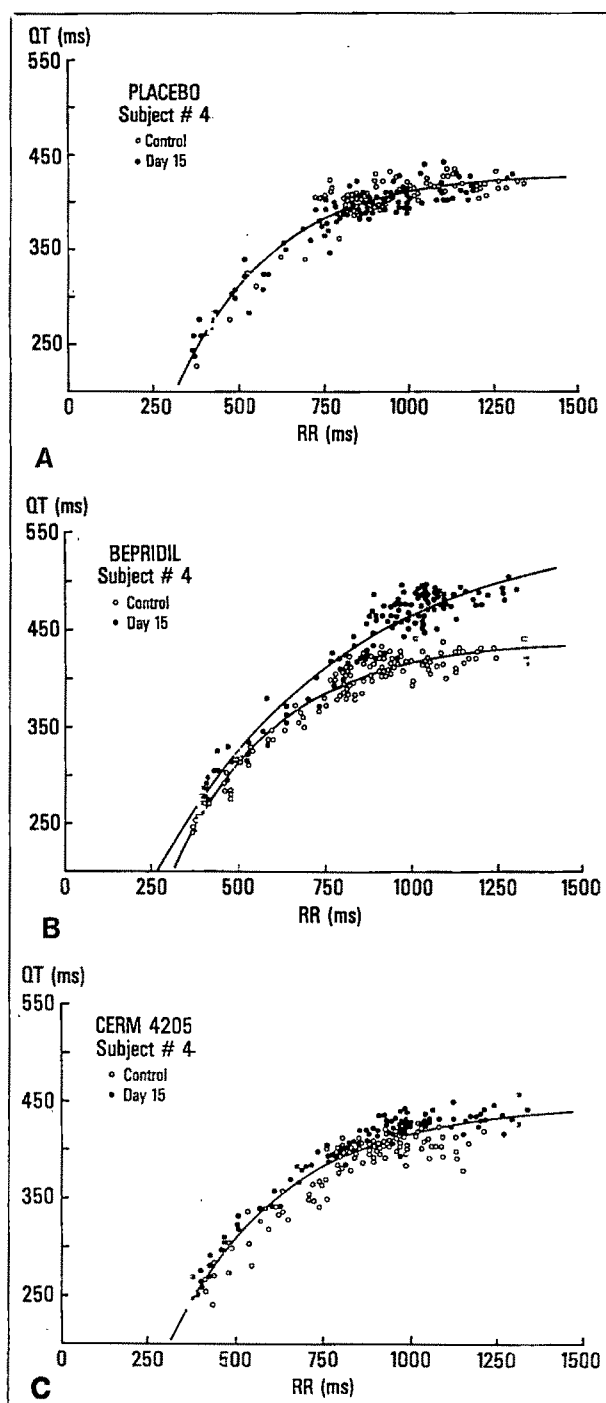


FIGURE 2. Effects of the 3 treatments on the QT-RR relation in 1 representative subject.

server using a digitizing pad (Houston TM 17, precision ± 0.4 mm) interfaced with a Victor S1 microcomputer. The QT interval was measured from the initial downward deflection of the QRS complex to the end of the T wave determined by the criteria described by Lepeschkin and Surawicz.¹³

Data analysis: The relations between QT and RR were studied separately for each subject using approximately 200 individual data points obtained during rest and exercise recordings. Collected data points were fitted to the exponential equation $QT = A - B \cdot \text{Exp}(-k \cdot RR)$, where A, B and k are regression parameters by using a nonlinear regression analysis program, described previously by Sarma et al.⁹ The individual equations thus obtained were compared by means of covariance analysis, which permitted comparison of control periods (day 0), determination of the effects of each treatment (comparison between day 0 and day 15), and comparison of the effects of the different treatments (day 15). In addition, calculated QT values were derived from individual nonlinear QT-RR relations for the following RR values: 500, 750, 1,000, 1,250 and 1,500 ms. These individual calculated QT values were averaged and the effects of treatments were compared by analysis of variance.

To assess the effects of the pharmacologic tests (isoproterenol and/or atropine) on QT interval, all individual QT data measured during each different test were pooled and averaged for the following measured RR interval values: 500 ± 2 , 550 ± 2 , 600 ± 2 , 650 ± 2 and 700 ± 2 ms. Analysis of variance and paired *t* tests were used to compare these mean measured QT values during the pharmacologic tests before and after administration of each of the 3 treatments.

Statistical significance was defined as $p < 0.05$.

RESULTS

Cardiovascular resting parameters: Heart rate, systolic and diastolic blood pressure and electrocardiographic intervals (PR, QRS and QT) measured at rest did not significantly differ between the 3 control periods on day 0 (Table I). On day 15, after administration of bepridil and CERM 4205 for 2 weeks, heart rate and systolic and diastolic blood pressure were not significantly altered compared with placebo. The duration of PR and QRS intervals did not change significantly with any of the 3 treatments. QT interval duration was not altered after administration of placebo or CERM 4205 compared with the control value (Table I). By contrast,

bepridil significantly lengthened QT. This effect was significant on day 7, and increased until day 15 (Figure 1). These bepridil-induced changes in QT were not significantly correlated with bepridil plasma concentrations.

QT-RR relation: PHYSIOLOGIC QT-RR RELATION: QT interval duration and preceding cardiac cycle length (RR) were fitted in each subject to an exponential equation: $QT = A - B \cdot \exp(-k \cdot RR)$ before and after each period of treatment (placebo, bepridil and CERM 4205). Table II summarizes the mean regression parameters of this equation during each control period (day 0) and after 15 days of each treatment (day 15). Covariance analysis showed that the values obtained for the 3 control periods were similar and that the individual QT-RR relation was stable over time.

On day 15, the individual QT-RR relations remained monoexponential. We observed no significant change in QT adaptation to RR duration during either placebo or CERM 4205. By contrast, the QT-RR relation was significantly altered during the bepridil period, with an upward shift of the curve compared with the control period. Figure 2 illustrates these differences in 1 representative subject. The asymptote A of the exponential equation, which may reflect a theoretical maximal QT value, was significantly higher with bepridil than with placebo or CERM 4205 on day 15 (Table II).

The drug-induced percent changes in calculated QT intervals for various cardiac cycle lengths are shown in Figure 3. Neither placebo nor CERM 4205 lengthened the QT interval at any heart rate while bepridil induced a significant prolongation in QT at RR intervals ≥ 750 ms. This lengthening in QT was rate-dependent and increased when heart rate was slower since QT interval increased by $10 \pm 4\%$ at RR of 750 ms, $12 \pm 6\%$ at RR of 1,000 ms, $14 \pm 8\%$ at RR of 1,250 ms and $15 \pm 9\%$ at RR of 1,500 ms ($p < 0.05$).

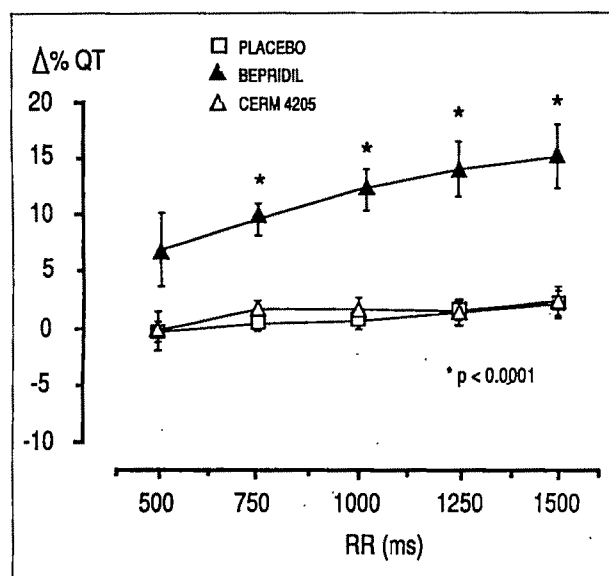


FIGURE 3. Mean percent changes in calculated QT intervals compared with control values during each of the 3 treatments ($n = 12$, mean \pm standard error of the mean).

Effects of pharmacologic tests: Pharmacologic tests including β -adrenergic stimulation (isoproterenol), parasympathetic blockade (atropine) and β -adrenergic stimulation under parasympathetic blockade were performed before (day 0) and after (day 15) each treatment period.

On day 0, before any drug administration, incremental intravenous bolus doses of isoproterenol resulted in a shortening in RR intervals but, in response to this isoproterenol induced-tachycardia, QT did not decrease to the same extent as was the case during exercise-induced tachycardia. During bepridil, similar results were obtained; however, at RR values ≤ 600 ms, isoproterenol

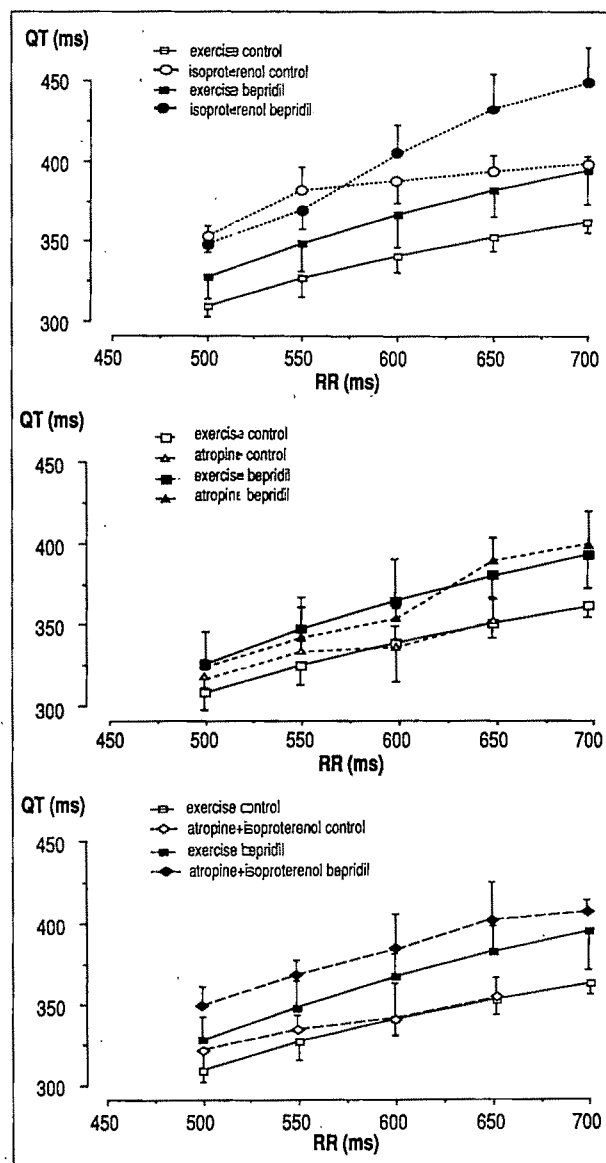


FIGURE 4. Effects of pharmacologic interventions (broken line) on the measured QT versus RR relation compared with physiologic situation (exercise) (solid line) before (open circles) and after (closed circles) bepridil (mean \pm standard deviation). Top panel, β -adrenergic stimulation (isoproterenol); middle panel, parasympathetic blockade (atropine); bottom panel, β -adrenergic stimulation after parasympathetic blockade (isoproterenol + atropine).

suppressed bepridil-induced prolongation of QT (Figure 4, upper panel). After atropine IV injection, before and after bepridil administration, the adaptation of QT interval to sinus cycle length was similar to that obtained during exercise (Figure 4, middle panel). When the isoproterenol test was performed after atropine injection, before and after bepridil administration, the QT adaptation to the tachycardia induced by isoprenaline and atropine did not significantly differ from the QT-RR adaptation during exercise (Figure 4, lower panel).

Neither placebo nor CERM 4205 significantly changed the effects of atropine and/or isoproterenol on QT interval compared with the predrug period.

Plasma levels of bepridil and CERM 4205: Changes in mean minimal plasma concentrations of CERM 4205 and bepridil over time are shown in Figure 5. Steady state of plasma concentrations were reached by the seventh day of treatment for both drugs, and minimal plasma concentrations (12 hours after dosing) averaged $600 \pm 260 \text{ ng} \cdot \text{ml}^{-1}$ for bepridil and $58 \pm 35 \text{ ng} \cdot \text{ml}^{-1}$ for CERM 4205.

DISCUSSION

The results of this study in healthy volunteers have shown that bepridil did not alter resting heart rate and blood pressure, exerted no effect on PR and QRS intervals, but caused a significant prolongation of QT interval. This increase was the most on day 15 and was not correlated with the increase in plasma concentrations of the compound noted between days 0 and 15. CERM 4205 had no effect on heart rate, blood pressure or electrocardiographic intervals. The adaptation of QT to the preceding cardiac cycle length was of a monoexponential type for all subjects in physiologic conditions of rest and exercise. This relation was stable over time within the 3 control periods and remained exponential after 14 days of treatment with placebo, bepridil or CERM 4205 treatment. CERM 4205 did not alter the QT-RR relation. However, bepridil induced a rate-dependent in-

crease in QT interval, and the individual exponentials calculated on day 15 of the bepridil period differed from those of the control periods.

After β -adrenergic stimulation with isoprenaline, QT no longer adapted to changes in heart rate. After atropine, the tachycardia induced by the vagolytic effect did cause physiologic adaptation of QT and, after subsequent β -adrenergic stimulation, QT adapted to changes in heart rate. Placebo and CERM 4205 did not alter the changes in QT induced by atropine and isoprenaline. However, with bepridil, QT was significantly more prolonged than it was with the 2 other treatments for successive doses of isoprenaline before and after atropine administration.

The results of this study, showing that bepridil did not affect either PR or QRS but significantly prolonged QT interval, are in agreement with other studies in healthy volunteers⁴ or in patients.^{1,14-16} None of these studies has been able to demonstrate a plasma concentration-effect relation.⁴⁻⁶ In this study, minimal plasma levels were about 10 times greater for bepridil than for CERM 4205. These results are consistent with previous pharmacokinetic studies of both drugs, and the difference in plasma levels can be explained mainly by the fact that bepridil, with a 5 times longer elimination half-life than CERM 4205, accumulates in the body much more than CERM 4205 does. However the 200 mg twice-daily dosing regimen of bepridil has been demonstrated to be effective in patients with angina pectoris¹⁷ and preliminary results with CERM 4205 have shown that this dosage was effective in the same population of patients (data on file, Organon Laboratory).

In addition to its action on the calcium current,^{18,19} bepridil has been shown to exert an inhibitory effect on the fast sodium channel (a class I antiarrhythmic effect).²⁰ Furthermore, bepridil has been shown to decrease the potassium outward current,²¹ which is likely to explain the delay in ventricular repolarization. These latter 2 properties, added to the bradycardiac effect, account for the role of bepridil in the genesis of torsades de pointes.^{6,7} Leclercq et al⁶ showed that in all cases of bepridil-induced torsades de pointes, sinus bradycardia was present. For the purpose of evaluating and monitoring the effects of drugs on ventricular repolarization, cardiologists and pharmacologists need a way of describing the relation between cardiac cycle length and the duration of ventricular repolarization, i.e., a theoretical normal QT for every value of RR. To date, the current methods of correcting QT according to heart rate are inadequate and may lead to a false interpretation of the effects of drugs that simultaneously alter heart rate and ventricular repolarization.²² Recently, an exponential model has been demonstrated to best describe the individual relation between QT and RR.⁹⁻¹¹ The calculation of QT using individual exponential equations before and after treatment permits one to study the effects of drugs by comparing the calculated QT values for various RR intervals between treatments. No study to date has investigated the effects of bepridil

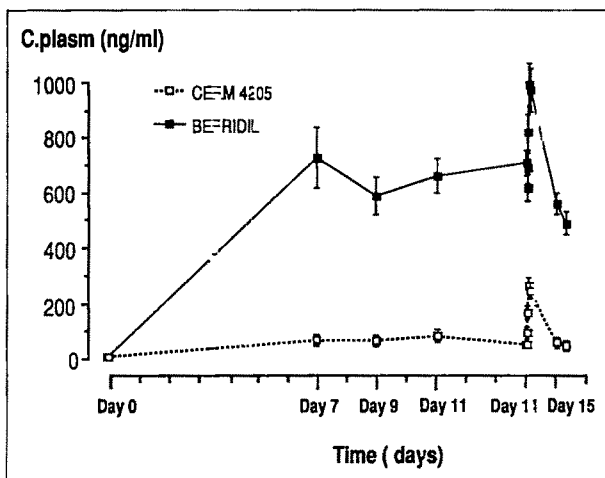


FIGURE 5. Changes in mean plasma concentrations of CERM 4205 and bepridil over time ($n = 12$, mean \pm standard error of the mean).

on QT interval over a wide range of physiologic heart rates. Our results show that bepridil, by lengthening QT, altered the physiologic relation between QT and RR, whereas this relation remained unchanged during the 2 weeks after treatment with CERM 4205. During exercise, tachycardia caused a shortening in QT and the effects of bepridil were no longer apparent. However, when heart rate decreased, the RR interval increased and the QT lengthening due to bepridil increased. These results are consistent with other studies that have already demonstrated the rate dependence of the lengthening in action potential duration for class III antiarrhythmic drugs like quinidine²³ and sotalol.²⁴ The prolongation of action potential duration with such drugs could be observed at all stimulation frequencies but the effects increased at low stimulation rates. These results correspond to a reverse use dependence compared with the action of antiarrhythmic drugs operating on the sodium and calcium channels (class I and IV) whose effects are enhanced at increasing stimulation rates. One hypothesis, concerning the ionic mechanisms that could explain such a rate dependence of class III antiarrhythmic effects, has been proposed by Hafner et al.²⁴ For potassium channels, in contrast to sodium and calcium channels, it is not the frequency of channel activations that may determine use dependence but rather the integral open time, which is strongly controlled by action potential duration. Long action potentials involve a higher probability for the drug to operate on activated channels. Because action potentials are prolonged by reducing stimulation frequency, the effects of these drugs should be enhanced under these conditions. These findings may explain the occurrence of torsades de pointes, since, in the presence of bradycardia, QT lengthening during bepridil treatment is increased.

Beta-adrenergic stimulation neither shortened nor lengthened QT when RR decreased. This finding confirms that of our earlier study¹⁰ but contradicts the results of Kawataki et al.²⁵ who reported that, after isoprenaline at the dose of 0.4 µg/min, QT shortening followed that of RR to an even greater degree than during exercise. However, Abildskov²⁶ showed that rapid injections of catecholamines in the anesthetized dog resulted in QT prolongation, whereas slow infusions shortened QT. In our study, however, isoprenaline, when it induced tachycardia >100 beats/min, caused QT shortening, even during bepridil treatment. On the other hand, the vagolytic effects of atropine resulted in a greater shortening of QT even during bepridil treatment. These findings show that the administration of isoprenaline to suppress bepridil-induced sinus bradycardia needs a dosage high enough to cause a tachycardia of >100 beats/min to shorten QT interval. Atropine injection could be an alternative drug to prevent bradycardia-induced torsades de pointes after bepridil administration.

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Are Electrophysiologic Studies Indicated in Nonsustained Ventricular Tachycardia?

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Electrophysiologic studies are frequently used in the evaluation and treatment of patients with sustained ventricular arrhythmias. One randomized study has demonstrated the superiority of electrophysiologically guided therapy to Holter guided therapy in these patients,¹ and a second, larger, multicenter trial is underway.² As electrophysiologic studies have become more widely available, increasing numbers of patients with nonsustained ventricular tachycardia (VT), a very common arrhythmia associated with sudden and non-sudden cardiac death,³ are being referred for invasive evaluation. This editorial will examine the usefulness of electrophysiologic studies in this group of patients.

Table I lists the findings of studies that have reported the results of programmed stimulation in patients with nonsustained VT. These studies differ in (1) nature of underlying heart disease, (2) stimulation protocol, and (3) definition of a positive study.

It is clear from Table I that patients without diagnosable organic heart disease have a low rate of inducibility. Because of the favorable prognosis in this group, electrophysiologic studies are only rarely indicated. Patients with heart disease not related to coronary artery disease, particularly idiopathic cardiomyopathy, have an intermediate rate of inducibility. These patients have been demonstrated to have a propensity for sudden cardiac death that is not predicted by the response to programmed stimulation, and electrophysiologic study is unlikely to be of major usefulness in this group.^{3,18} Patients with coronary artery disease, specifically those with impaired left ventricular function and areas of akinesia/dyskinesia, have a higher rate of inducibility and are the most likely group to benefit from electrophysiologic study.

The ideal stimulation protocol for patients with nonsustained VT is unknown. Triple extrastimuli markedly increase the yield of sustained VT,⁴ suggesting that less aggressive protocols may misclassify patients. However, triple extrastimuli will inevitably lead to the induction of some arrhythmias that are not clinically relevant.^{10,11}

As more aggressive stimulation protocols are used, greater attention must be paid to the definition of a positive study. Whereas the goal of electrophysiologic study in sustained VT is reproduction of the clinical arrhythmia, the goal in patients with nonsustained VT may be to expose a latent sustained arrhythmia. How-

ever, the definition of a positive study has not been uniformly agreed upon. Induction of sustained monomorphic VT has generally been considered a positive response. Whereas induction of sustained monomorphic VT indicates a substrate capable of maintaining an arrhythmia, it may not reliably indicate that the arrhythmia would occur clinically in this population. Induction of nonsustained polymorphic VT or ventricular fibrillation has generally not been considered a positive response. Although these arrhythmias may represent a nonspecific response to aggressive stimulation,^{10,11} in some patients they may indicate a clinically relevant unstable tachycardia mechanism.¹² The significance of induced monomorphic nonsustained VT is unclear.

Table II lists studies that examined the role of programmed stimulation in the clinical management of patients with nonsustained VT. These studies address 2 distinct questions: (1) Can electrophysiologic studies select a low-risk, noninducible group that does not require antiarrhythmic therapy? (2) Are electrophysiologic studies useful for selecting therapy in inducible patients? Gomes,¹³ Zheutlin,¹⁴ and their co-workers reported that inducible patients had a low risk of arrhythmic events. These studies are difficult to interpret because they (1) included both patients with nonsustained VT and complex ectopy, (2) included patients with a range of underlying heart disease including both normal hearts and idiopathic cardiomyopathy, and (3) used a relatively unaggressive stimulation protocol that undoubtedly included patients in the noninducible group who would be inducible with more aggressive protocols. Buxton,¹⁵ Klein and Machell,¹⁶ Manolis and Estes,¹⁷ Hammill,¹⁸ and their co-workers studied more homogeneous populations of patients with coronary artery disease with more aggressive stimulation protocols that included triple stimuli. However, differences exist between these studies in: (1) definition of clinical nonsustained VT, (2) percentage of patients with presyncope or syncope, (3) stimulation protocol, and (4) definition of a positive study. Buxton, Klein, Manolis and their co-workers¹⁵⁻¹⁷ suggest that patients with coronary artery disease who are noninducible do well without antiarrhythmic therapy. Hammill et al,¹⁸ in the only prospective study, did not confirm this finding. In addition, in the studies of Buxton, Klein, and Hammill,¹⁵⁻¹⁷ some noninducible patients were treated with antiarrhythmic drugs. Further studies with larger numbers of patients and longer follow-ups are needed.

Whether electrophysiologically guided therapy is advantageous for patients with inducible VT is difficult to determine. As seen in Table II, electrophysiologically selected therapy was deemed effective on follow-up in

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TABLE I Results of Programmed Stimulation in Patients with Nonsustained Ventricular Tachycardia							
Reference	Stim. Protocol	HD	No. of Pts.	%SuVT	%Vfib	%NSVT	Correlate of Inducibility
Buxton et al ⁴	S ₂ S ₃ (S ₄ , isoproterenol, LV)	CAD	33	39	0	36	Left ventricular aneurysm
		n-CAD	26	8	0	31	
		nl	24	0	0	29	
Veltri et al ⁵	S ₂ S ₃ (LV)	CAD	19	26	0	21	Structural heart disease
		n-CAD	10	20	0	30	
		nl	4	0	0	0	
Spielman et al ⁶	S ₂ S ₃ S ₄	CAD	30	50% 29%	17	32	Akinesia or aneurysm
		n-CAD	28				
Sulpizi et al ⁷	S ₂ S ₃ (S ₄ , LV)	CAD	38	19	0	45	LV dysfunction
		n-CAD	9	22	0	48	
		nl	12	0	0	48	
Furukawa et al ⁸	S ₂ S ₃ S ₄ S ₅	CAD	76	41	3	16	Akinesia/dyskinesia EF <40%

CAD = coronary artery disease; EF = ejection fraction; HD = heart disease; LV = left ventricle; n-CAD = noncoronary artery disease (i.e., cardiomyopathy or valvular disease); nl = normal; NSVT = nonsustained ventricular tachycardia; Stim. protocol = stimulation (parentheses indicate use in some but not all patients); SuVT = sustained ventricular tachycardia; Vfib = ventricular fibrillation.

82 to 93% of the small number of patients in these studies. Buxton et al¹⁵ and Klein and Machell¹⁶ compared these results with those in a group of inducible patients without electrophysiologically guided therapy. However, the groups without electrophysiologically guided therapy were not comparable because they included a much higher percentage,¹⁵ or even all,¹⁶ of the patients for whom no effective drug could be found at electrophysiologic study. Whether electrophysiologically guided therapy is superior to Holter-guided, empiric or no therapy is not known.

Electrophysiologic studies have helped us appreciate the complexity of nonsustained VT. Electrophysiologic studies, despite their limitations, may be clinically useful in certain subsets of patients, i.e., those with syncope and those with infrequent relatively prolonged episodes.

However, further studies are needed before widespread application of electrophysiologic studies to patients with nonsustained VT can be recommended.

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TABLE II Clinical Application of Electrophysiologic Studies in Patients with Nonsustained Ventricular Tachycardia											
Reference	Arrhythmia	HD	%PS/S	Stim. Protocol	Positive Study	F/U (mo)	Noninducible		Inducible EP Rx		Inducible Non-EP Rx
							n	%Arrhythmia free	n	%Arrhythmia free	n free
Gomes et al ¹³	Low III-8%	CAD-77%	0	S ₂ S ₃	SuVT	30	51	98	19	68	—
	Low IV-41%	n-CAD-14%			VF						—
Zheutlin et al ¹⁴	Low IV-51%	nl-10%	0	S ₂ S ₃	≥5 beat NSVT	22	52	100	32	88	—
	Low IV-82%	n-CAD-44%			≥6 beat NSVT						—
Buxton et al ¹⁵	≥3 beat VT	CAD-100%	29	S ₂ S ₃ S ₄	SuVT Symptomatic NSVT	28	26	96	18	89	10 50
Klein and Machell ¹⁶	≥5 beat VT	CAD-100%	13	S ₂ S ₃ S ₄	SuVT	14	18	100	11	82	11 36
					≥5 beat monomorphic NSVT						
Manolis and Estes ¹⁷	≥3 beat VT	CAD-100%	71	S ₂ S ₃	SuVT	21	31	97	21	100	—
					VF						—
Hammill et al ¹⁸	≥3 beat VT	EF <40-CAD 100%*	0	S ₂ S ₃ S ₄	≥6 beat NSVT monomorphic or polymorphic	15	14	79	14	93	—

* Only this group was used for analysis.

EP Rx = therapy selected by serial electrophysiologic studies; F/U = follow-up; non-EP Rx = therapy not selected by electrophysiologic study; nsr = normal sinus rhythm; %PS/S = % with presyncope or syncope. Other abbreviations as in Table I.

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Effect of Left Ventricular Ejection Fraction on Malfunctioning St. Jude Medical Prosthesis in the Aortic Valve Position

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Abnormal transvalvular flow due to partial or complete obstruction of the outflow orifice or the mobile element, and valve leaks due to valvular or paravalvular lesions, are the 2 main types of prosthetic valve dysfunction. Quantitative Doppler echocardiography has been used for assessing transprosthetic flow characteristics and pressure gradients.¹⁻⁵ In addition to prosthetic size, left ventricular (LV) function may be another important factor in assessing transprosthetic hemodynamic parameters. In a previous report of ours⁶; we assessed 74 patients with normally functioning St. Jude medical (SJM) prostheses in the aortic valve position by using Doppler echocardiography and found that a depressed LV ejection fraction resulted in corresponding changes in Doppler-derived transprosthetic hemodynamic measurements. The study evaluates the effect of LV function on Doppler-derived hemodynamic indexes in abnormally functioning SJM prostheses in the aortic valve position.

From January 1985 to June 1988, 13 patients with malfunctioning SJM prostheses in the aortic valve position were confirmed by cardiac catheterization and/or reoperation and with high-quality cardiac images and Doppler flow spectral signals; they were included for quantitative analysis (Table I). There were 9 men and 4 women aged 21 to 84 years (mean 56 ± 21). Prosthetic sizes ranged from 19 to 27 mm. Ten (77%) patients had valvular and/or paravalvular leaks and significant regurgitation proven by cineangiography and 7 underwent reoperation. The postoperative interval was 1.6 ± 2.8 years (range 1 week to 4.8 years).

Doppler echocardiography was performed using Irex Meridian phased array or Interspec XL mechanical ultrasound systems with pulsed and continuous mode Doppler (2.0 MHz) transducers. LV ejection fraction was measured from end-diastolic and end-systolic volumes determined by the microprocessor-controlled digitized planimeter of tracings from 2 orthogonal apical views and using biplane Simpson's rule method.⁷ The velocity profile across the aortic valve prosthesis was obtained from apical, right parasternal or suprasternal views. Peak velocity was the highest value recorded from multiple views. Peak pressure gradient (Δp) was estimated from the peak transvalvular velocity (V) using the simplified Bernoulli equation ($\Delta p = 4V^2$). The mean velocity and mean pressure gradient, time of flow and

acceleration were calculated using commercially available hardware and software. Velocity time integral was calculated by multiplying the mean velocity and time of flow and dividing by \sqrt{RR} to correct for heart rate. For all patients, 3 to 5 cardiac cycles were measured and averaged. In 2 patients with atrial fibrillation, ≥ 6 cardiac cycles were measured.

Results were expressed as the mean \pm standard deviation. Statistically significant differences between different groups were determined using the unpaired *t* test or chi-square test where appropriate. Statistical correlation between Doppler-derived measurements and prosthetic size was made using linear regression analysis. A *p* value ≤ 0.05 was considered statistically significant and that of < 0.10 marginally significant.

Doppler echocardiographic measurements in the 13 patients are listed in Table I. Five patients had normal (≥ 0.51) LV ejection fraction (group A) and 8 patients had depressed (< 0.51) ejection fraction (group B). Another 72 (with comparable prosthetic sizes from 19 to 27 mm and ages 62 ± 15 years) of 74 patients with normally functioning SJM prostheses in the aortic valve position were used as control subjects; 33 patients (control group A) had normal ejection fraction and 39 patients (control group B) had depressed ejection fraction.

Table II lists Doppler-derived transprosthetic hemodynamic measurements in patients with malfunctioning SJM prostheses in the aortic valve position compared to control subjects in relation to normal or depressed LV ejection fraction. Peak (51 ± 15 mm Hg) and mean (27 ± 9 mm Hg) pressure gradients in group A patients with malfunctioning prostheses and normal ejection fraction were higher than in group B patients with depressed ejection fraction or patients with normally functioning prostheses regardless of LV function. Similarly, corrected velocity time integral measurements in group A patients were significantly higher than those in both control group patients ($p < 0.05$). Significant differences for pressure gradients and corrected velocity time integral measurements were also found between group B and control group B patients (both with depressed ejection fraction) and abnormal and normal prostheses, respectively ($p < 0.025$ to 0.001). However, no significant differences for these Doppler-derived transprosthetic hemodynamic indexes were found between the mean values of group B and control group A patients. There were no significant differences for acceleration measurements between different groups.

Interobserver variability for quantitative measurement of peak pressure gradient assessed in 47 patients between 2 independent observers was $4.4 \pm 4.0\%$, where-

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TABLE I Clinical Characteristics, Hemodynamics and Doppler Echocardiographic Measurements in 13 Patients with Malfunctioning St. Jude Aortic Valve Prostheses

Age (yrs) & Sex	Prosthetic Size (mm)	Degree of AR (0 to 3 ⁺)	Doppler Echocardiography				
			PSG (mm Hg)	MG (mm Hg)	VTIC (m)	Acc (m/s ²)	LVEF
71M	23	3 ⁺	44	26	0.768	28	0.61
41M	29	1 ⁺	64	38	0.841	53	0.60
58F	23	(P-P abscess)	29	15	0.357	83	0.55
84F	19	3 ⁺	55	23	0.483	116	0.53
28M	23	1 ⁺	64	33	0.540	131	0.51
72F	21	3 ⁺	46	28	0.625	90	0.49
58M	27	2 to 3 ⁺	27	13	0.384	45	0.43
45M	25	3 ⁺	41	23	0.484	74	0.43
37M	25	2 ⁺	36	21	0.528	82	0.40
83M	23	3 ⁺	29	16	0.532	106	0.37
81F	19	2 to 3 ⁺	36	16	0.468	53	0.31
21M	25	2 to 3 ⁺	46	25	0.552	45	0.30
49M	23	2 to 3 ⁺	19	10	0.330	43	0.23

Acc = acceleration; AR = aortic regurgitation; LVEF = left ventricular ejection fraction; MG = mean pressure gradient; P-P = paraprosthetic; PSG = peak systolic gradient; VTIC = corrected velocity time integral.

TABLE II Comparison of Doppler-Derived Transprosthetic Hemodynamic Measurements Between Patients with Malfunctioning or Normally Functioning Prostheses in Relation to Normal or Depressed Left Ventricular Ejection Fraction

Group	PSG (mm Hg)	MG (mm Hg)	VTIC (m)	Acc (m/s ²)	HR beats/min
A	51 ± 15*†	27 ± 9†	0.598 ± 0.202†	82 ± 43	34 ± 25
B	35 ± 10§	19 ± 6§	0.488 ± 0.094§	67 ± 24	36 ± 12
Control A	32 ± 13	16 ± 6	0.458 ± 0.124	86 ± 48	77 ± 11
Control B	22 ± 8	11 ± 4	0.389 ± 0.110	53 ± 23	39 ± 15

p < 0.05 to 0.001.
* A versus B; † A versus control group A or B; ‡ p < 0.1, A versus B; § B versus control group B.
HR = heart rate; other abbreviations as in Table I.

as the intraobserver variability for ejection fraction assessed in 30 patients was $9 \pm 1\%$ in our previous study.⁶

Doppler-derived aortic transprosthetic velocity and pressure gradient is dependent on several factors. In addition to valve size, LV function is important. In many previous studies,¹⁻⁴ LV function was not considered. The findings in recent studies^{5,6} showed that the assessment of normally functioning prostheses can be improved by evaluating both LV ejection fraction and prosthetic size. Data in this study further confirm that in patients with malfunctioning valve prostheses, a depressed ejection fraction resulted in corresponding decreases in Doppler-derived transprosthetic pressure gradients and corrected velocity time integral measurements. Patients with abnormal aor-

tic valve prostheses and normal ejection fraction had the highest Doppler-derived pressure gradients and corrected velocity time integral measurements. Doppler indexes were similar in patients with a normal prosthesis and normal LV function and in patients with prosthetic malfunction and depressed LV function. In patients with depressed LV function, Doppler indexes were higher in prostheses functioning abnormally. Therefore, it is necessary to evaluate LV function and baseline and serial follow-up Doppler studies to detect prosthetic valve dysfunction.

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Analysis of Heart Rate Changes in Cardiac Transplant Recipients Related to Graft Rejection

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In this report we describe our observations regarding a decrease in spontaneous donor resting heart rate (HR) that correlates with histologic evidence of allograft rejection in a group of 42 patients after orthotopic cardiac transplantation. The study was designed to test the null hypothesis that there would be no difference in HR between the rejection and no-rejection groups.

Data from 42 patients (38 men, 4 women, donor age 27.6 ± 8 years, recipient age 43.3 ± 10 [mean \pm standard deviation]) were suitable for retrospective analysis. The classic orthotopic operative technique of Lower and Shumway was used in all patients. With cardiac transplantation, the donor atrium is denervated and remains so indefinitely.¹ Standard immunosuppressive therapy consisted of prednisolone, azathioprine, cyclosporine A and antithymocyte globulin. Weekly endomyocardial biopsies are done at our center in the first month, starting in the first week after transplantation, and a standard 12-lead surface electrocardiogram is recorded routinely on the day of biopsy. This is usually done after the biopsy with the patient at rest. The HR was calculated from 10 consecutive RR intervals. Because the donor heart is surgically denervated, there was considerable little variation in the HR at rest. Biopsy results were graded according to Billingham (no-mild-moderate-severe).² To standardize the number of data points in each patient, only measurements obtained within the first 4 weeks after transplantation were considered for analysis. Patients with atrial arrhythmias, permanent pacemakers and patients receiving any medication exerting direct or indirect chronotropic effects (antihypertensives) were excluded. Finally, a total of 141 biopsy results with concomitant HR measurements were available for analysis. There were 4 consecutive data points in 24 patients, 3 in 9 patients and 2 in 9 patients.

Comparisons were done by unpaired Student's *t* test and by 1-way analysis of variance followed by Scheffe's multiple-range comparison test, as appropriate.

Of the 141 biopsies corresponding to HR measurements, 67 were classified as no rejection and a total of 74 were classified as either mild ($n = 61$), moderate ($n = 12$) or severe ($n = 1$) rejection. HR measurements were pooled in the rejection group ($n = 74$) versus the no rejection group ($n = 67$) and the results are listed in Figure 1. The mean HR was 92 ± 11 beats/min (median 94, range 57 to 115) for the group showing no rejection and 86 ± 14 (median 89, range 51 to 110) in the group

with histologic evidence of rejection ($p = 0.005$). Confidence limits ($\pm 95\%$) ranged from 89 to 95 beats/min in the no rejection group and from 82 to 89 beats/min in the rejection group.

Arranging the HR into subgroups according to the grade of rejection revealed significant ($p < 0.05$) differences in HR between the group graded moderate rejection when compared with the group without histologic evidence of rejection (Table I).

A significant decrease in donor HR during cardiac allograft rejection was found. Moreover, the HR seems to reflect the severity of the rejection process (Table I). Our data are consistent with currently evolving concepts of an altered automaticity of pacemaker tissue during episodes of cardiac allograft rejection.^{3,4} Our findings are also in accordance with earlier observations of Jose,⁵ who found a decrease of the intrinsic HR (the HR obtained after

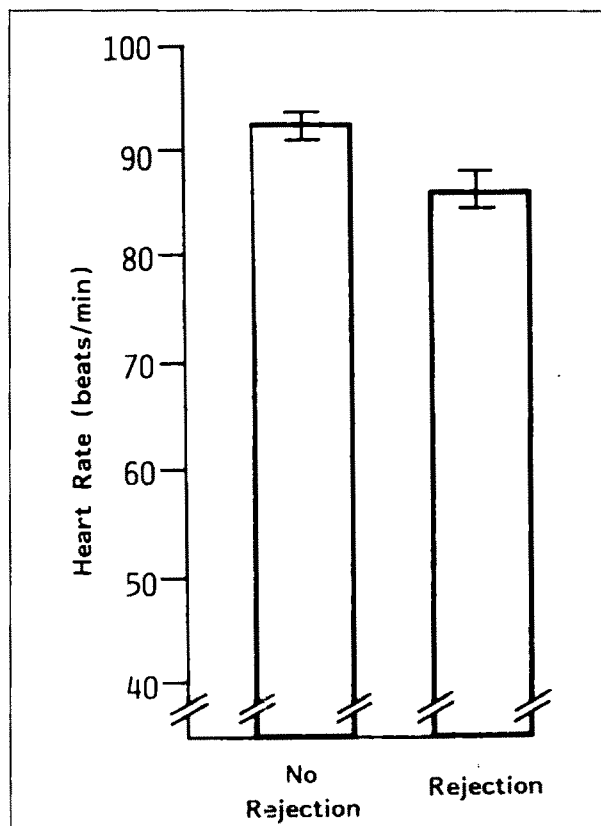


FIGURE 1. The sinus rate in cardiac transplant recipients free of rejection (a total of 67 biopsy results with concomitant heart rate measurements in 42 patients) versus those with mild, moderate or severe rejection pooled in 1 group ($n = 74$). Differences are statistically significant ($p = 0.005$). Data are mean \pm standard deviation.

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TABLE I Changes in Spontaneous Donor Heart Rate Related to Cardiac Allograft Rejection

Grade of Rejection	n	HR (beats/min)		Confidence Limits of HR (beats/min)	
		Mean \pm SD	Median/Range	-95%	+95%
No	67	92 \pm 11	94 57 to 115	89	95
Mild	61	88 \pm 13	90 52 to 110	84	91
Moderate	12	77 \pm 19*	72 51 to 109	65	89
Severe	1	70	—	—	—

* $p < 0.05$ (Scheffe test) versus follow-ups without histologic evidence of rejection.
HR = spontaneous resting heart rate; SD = standard deviation.

pharmacologic autonomic blockade) in a variety of cardiac disorders.

Major determinants of HR other than rejection were probably not of importance in our study group for 3 reasons. First, patients receiving antihypertensive drugs were excluded. Second, the effect of circulating catecholamines may be neglected in view of the resting conditions before and during registration of the electrocardiogram; circulating catecholamines in cardiac transplant recipients, however, have been found to increase only in response to greater work loads.⁶ Third, neural autonomic influences are not of importance since the transplanted

human heart is surgically denervated and remains so indefinitely.¹

The precise mechanism of the observed phenomenon remains to be determined. Local release of adenosine is currently under discussion as a possible mechanism for negative chronotropy in cardiac rejection.⁴ However, a decrease in HR might be caused by local edema or the cellular infiltrate itself as well; an increase in intercellular coupling resistance or capacitance would clearly increase the spontaneous sinus cycle length.⁷

Future studies should be directed at confirming our observation and at evaluating possibilities of standardization to make use of this principle in a clinical setting.

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Failure of Trifluoperazine to Resolve Spontaneous Echo Contrast Evaluated by Transesophageal Echocardiography

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Spontaneous echo contrast, the echocardiographic appearance of discrete, smoke-like intracavitary reflections, was described for the first time in 1975 by Feigenbaum et al.¹ Since the introduction of transesophageal echocardiography and the usage of higher frequency transducers, it is a well recognized phenomenon, which occurs in conditions with diminished blood flow velocities. Transesophageal echocardiography has shown its superiority to the transthoracic ultrasound approach, especially for assessment of spontaneous echo contrast in the left atrium. The exact pathophysiologic mechanism responsible for occurrence of spontaneous echo contrast is not known. Erbel et al² found increased platelet aggregation in patients with spontaneous echo contrast. It has been shown that spontaneous echo contrast is involved with an increased risk of embolic events.³ It is therefore the therapeutic aim to effect its resolution.

Trifluoperazine is a substance with documented properties for inhibition of platelet aggregation by selectively binding calmodulin, which activates platelet phospholipase A₂. Additionally, it disaggregates existing platelet aggregates.⁴ Recently, the successful application of trifluoperazine for resolution of spontaneous echo contrast seen by transthoracic echocardiography has been described in a case report in this journal.⁵ We prospectively investigated the effect of oral trifluoperazine on spontaneous echo contrast using transesophageal echocardiography in 5 patients.

Transthoracic and transesophageal echocardiography were recorded using a Hewlett Packard Sonos 500 (2.5 MHz transthoracic transducer, 5.0 MHz transesophageal echoscope). Patient data are listed in Table I. Four patients were investigated because of preceding embolic events during the last 3 months. By using transesophageal echocardiography, 4 patients showed spontaneous echo contrast within the left atrium, 2 of them suffered from left heart failure and 1 patient had a mitral valve prosthesis. One patient was in atrial fibrillation. In an additional patient with dilated cardiomyopa-

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TABLE I Patient Data

Pt	Age (yrs) & Sex	Concomitant Therapy	Rhythm	Clinical Diagnosis	LVEF (%)	History of Embolism	Localization of SEC	TGC Before Therapy (dB)	TGC After Therapy (dB)
1	66, M	heparin	AF	DC	20	Peripheral	LA + LV	10	10
2	47, F	coumarin	SR	MVP	55	Peripheral	LA	25	20
3	52, M	aspirin	AF	CAD	60	—	LA	25	30
4	60, M	—	AF	HC	25	Cerebral	LA	20	20
5	78, M	—	AF	CAD	25	Cerebral	LA	15	20

AF = atrial fibrillation; CAD = coronary artery disease; DC = dilated cardiomyopathy; HC = hypertrophic cardiomyopathy; LA = left atrium; LVEF = left ventricular ejection fraction; MVP = mitral valve prosthesis; SEC = spontaneous echo contrast; SR = sinus rhythm; TGC = time gain control.

thy, spontaneous echo contrast was detectable within the left atrium as well as in the left ventricular cavity. In no patient was thrombus formation or another source of cardiac embolization found by transthoracic and transesophageal echocardiography. Three patients were under

anticoagulation therapy when they were studied first by transesophageal echocardiography. One patient received heparin therapy (25,000 IU/day), 1 patient received aspirin (100 mg/day) and the remaining patient received coumarin (Quick's value of 25%). These therapeutic

FIGURE 1. Patient 4. *Left panel*, transesophageal echocardiogram frontal long-axis view of the heart. Spontaneous echo contrast in the left atrium (LA). No drug therapy (heparin, aspirin, coumarin or trifluoperazine) has been initiated. *Right panel*, same echocardiographic view and instrument settings after trifluoperazine therapy, showing no influence on spontaneous echo contrast density. Ao = aorta; LV = left ventricle; MV = mitral valve.

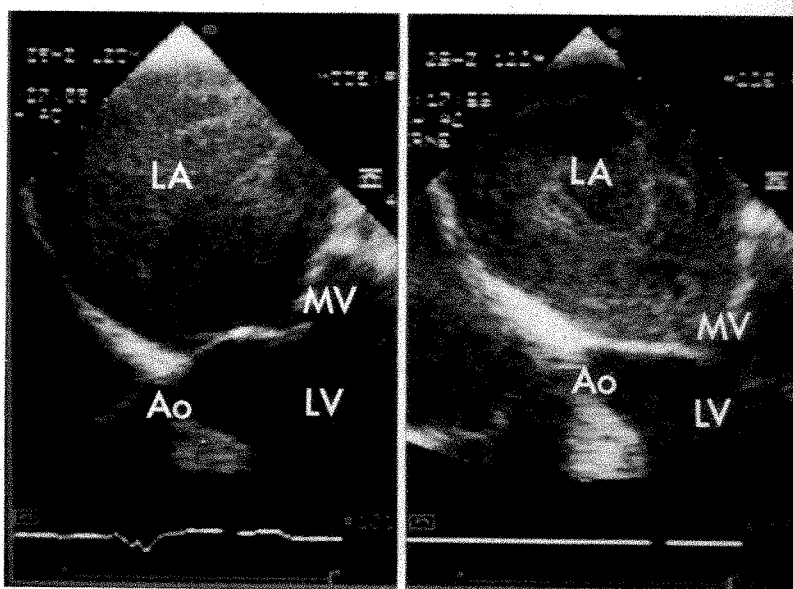
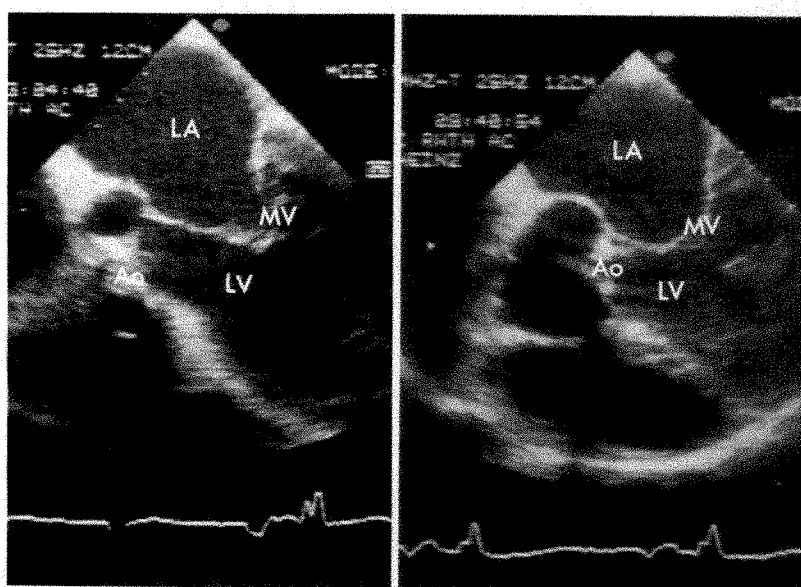


FIGURE 2. Patient 1. *Left panel*, transesophageal echocardiographic frontal long-axis view of the heart. Spontaneous echo contrast in left atrium (LA). The patient is receiving heparin therapy. *Right panel*, same echocardiographic view and instrument setting after addition of trifluoperazine therapy, showing no change in spontaneous echo contrast density. Ao = aorta; LV = left ventricle; MV = mitral valve.



regimens remained unchanged during the entire study period.

Two mg of trifluoperazine were given orally once a day for 5 consecutive days to all patients. To analyze the influence of trifluoperazine on spontaneous echo contrast detected by transesophageal echocardiography, quantification of its density before and after platelet disaggregating therapy was performed. To standardize the quantification of spontaneous echo contrast, density transit and compress were arbitrarily set at maximum. The minimal time gain control setting required for detection of spontaneous echo contrast was determined by 2 independent observers. For this purpose, time gain control at each penetration level was chosen to be the same. Spontaneous echo contrast density was reevaluated by a second transesophageal echocardiographic examination on the sixth day, one day after the last administration of trifluoperazine. Again, the minimal gain settings required for imaging of spontaneous echo contrast were evaluated.

Despite therapy with trifluoperazine, spontaneous echo contrast persisted in all 5 patients. Its density remained unchanged. The minimal time gain control setting for detection of spontaneous echo contrast was 19 ± 7 dB before and 20 ± 7 dB after treatment with trifluoperazine. As a monotherapy, trifluoperazine did not show any effect on spontaneous echo contrast formation (Figure 1). Trifluoperazine in combination with heparin, coumarin or aspirin did not effect any change in spontaneous echo contrast density either (Figure 2). An inhibiting effect of a combination therapy consisting of trifluoperazine with other platelet inhibitors or anticoagulants therefore seems to be unlikely.

By using transesophageal echocardiography, which is distinguished from the transthoracic approach by a high-

er sensitivity in detecting spontaneous echo contrast, we conclude that trifluoperazine in the given dosage is ineffective in abolishing or decreasing spontaneous echo contrast density. The positive effect of trifluoperazine on spontaneous echo contrast previously described might be a result from a nonidentical gain setting before and after the administration of the drug. The patient investigated by Mahony et al⁵ had had a myocardial infarction 11 days before the beginning of trifluoperazine therapy. Abnormal pulsed-wave Doppler flow patterns in the apical region of the left ventricle after myocardial infarction have been described recently.⁶ They must be interpreted as related to local flow disturbances. Therefore, it is not to be excluded that the detected change in spontaneous echo contrast density in the report by Mahony is related to alterations in local slow-flow phenomenon after myocardial infarction.

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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE

Hypertension

Lopressor tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris

Lopressor is indicated in the long-term treatment of angina pectoris.

Myocardial Infarction

Lopressor ampuls and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSE AND ADMINISTRATION, CONTRAINDICATIONS, AND WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSE AND ADMINISTRATION**).

CONTRAINDICATIONS

Hypertension and Angina

Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).

Myocardial Infarction

Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval \geq 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS

Hypertension and Angina

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute, a beta₂-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See **DOSE AND ADMINISTRATION**.)

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure

occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval \geq 0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure \leq 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta₁ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta₂-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should not be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta₂ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta₂ agonists may produce serious cardiac arrhythmias.

PRECAUTIONS

General

Lopressor should be used with caution in patients with impaired hepatic function.

Information for Patients

Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.

Laboratory Tests

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate carcinogenic potential. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increase in incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C

Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Lopressor is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Hypertension and Angina

Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.

Myocardial Infarction

Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	Placebo
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R \geq 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System

Reversible mental depression progressing to cataplexy; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE

Acute Toxicity

Several cases of overdosage have been reported, some leading to death.

Oral LD₅₀s (mg/kg): mice, 1158-2460; rats, 3090-4670.

Signs and Symptoms

Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A beta₂-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

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Cardioprotection
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In hypertension...angina...MI

Lopressor[®]
metoprolol tartrate

Tablets: 100 mg, 50 mg, Ampoules: 5 mg/5 ml

Contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.
Please consult Brief Summary of Prescribing Information on following page.

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